Independent and Joint Effects of Family History and Lifestyle on Colorectal Cancer Risk: Implications for Prevention[1]

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Abstract

It has been suggested that, for a substantial proportion of "sporadic" colorectal cancers (CRCs), inheritance determines individual susceptibility and that lifestyle determines which susceptible individuals express cancer. Because the genetic basis of this inherited susceptibility remains undefined, we used family history of the disease as a proxy for a genetic predisposition to examine its interactions with a variety of lifestyle factors in a large population-based case-control study of CRC. The subjects were 698 male and 494 female Japanese, Caucasian, Filipino, Hawaiian, and Chinese patients diagnosed with CRC in Hawaii during 1987–1991 and 1192 population controls matched to cases on age, sex, and ethnicity. Fourteen percent of the cases and 6% of the controls reported a family history of CRC among parents or siblings. After adjusting for other covariates, significant interactions with family history were found for beef and ethanol intakes in males ($P = 0.03$). Relative to men without a family history and whose intake fell in the lower third, odds ratios (ORs) for CRC for men with a family history and in the upper tertile of intake were 10.8 [95% confidence interval (CI), 4.2–27.6] and 7.5 (CI, 3.1–18.2) for beef and ethanol, respectively. The corresponding ORs for men without a family history and in the upper tertile were 1.5 (CI, 1.0–2.3) and 1.4 (CI, 1.0–1.9), respectively. No interactions were detected in women. Using a summary measure of lifestyle, we found that family history was not associated with CRC among men who were at the lower-risk tertile for all of the lifestyle risk factors. In contrast, the OR for men with a family history and at the higher-risk tertile for all of the lifestyle variables was 11.7 (CI, 5.8–23.9). In the absence of a family history, this OR was 4.8 (CI, 3.2–7.2). These data suggest that family history increases the risk of sporadic CRC in men mainly through its interaction with lifestyle exposures, primarily a high beef and ethanol intake, and are consistent with recent reports of effect modifications of dietary associations by metabolic genes. Computation of population attributable risks also suggested that a comprehensive reduction in exposure to lifestyle risk factors—and more specifically to ethanol and beef for individuals with a familial predisposition for the disease—may have a large beneficial effect on CRC incidence.

Introduction

It is estimated that about 130,000 new cases of CRC[3] are diagnosed each year in the United States. The two well-characterized syndromes with a Mendelian mode of inheritance, FAP and HNPCC, are expected to account for no more than 5% of all CRC cases. The remaining patients are usually considered to have "sporadic" disease. However, it is well established that sporadic cases cluster in families more often than expected (1, 2), which suggests the possibility of an inherited component. Pedigree analyses of selected kindreds have suggested that a partially penetrant autosomal dominant inheritance of susceptibility to colorectal neoplasia is common and may explain a substantial proportion of the cancers otherwise considered as sporadic (3, 4). In view of the known association of CRC with diet, it has been hypothesized that inheritance determines individual susceptibility to colonic neoplasm and that dietary factors, or other lifestyle factors, determine which susceptible individuals express cancer (4).

Although much is known about the lifestyle risk factors for CRC, the molecular genetic basis for this inherited susceptibility remains largely undefined. Nevertheless, it is possible to use family history of the disease as a proxy for a genetically determined predisposition. The aims of the present study were: (*a*) to identify specific lifestyle risk factors with a particularly strong effect on the CRC risk of individuals at increased familial risk for the disease; and (*b*) to assess the individual and joint effects of family history and a summary measure of lifestyle on CRC risk. We used the data from a large population-based case-control study of CRC to explore interactions between various lifestyle factors and family history of the disease among first degree relatives. We previously reported that, consistent with past data, such a history was associated with a 2.5-fold (95% CI, 1.8–3.4) increase in CRC risk in this study (2).

Methods

The study methodology is described in greater detail elsewhere (5). Briefly, the cases were identified in all of the main hospitals on the island of Oahu, Hawaii, by the rapid-reporting system of

Received 7/23/98; revised 10/19/98; accepted 10/29/98.
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[1] Supported in part by Grant PO1-CA-33619 and Contract NO1-CN-05223 from the National Cancer Institute.
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[3] The abbreviations used are: CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; OR, odds ratio; CI, confidence interval; NSP, nonstarch polysaccharides; AR, attributable risk; P:S, polyunsaturated fat:saturated fat; APC, adenomatous polyposis coli.

the Hawaii Tumor Registry, a member of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Eligible cases were all Oahu residents who were newly diagnosed with histologically confirmed adenocarcinoma of the large bowel between January 1987 and December 1991 and who were any percentage of Hawaiian ancestry or at least 75% Japanese, Caucasian, Filipino, or Chinese. Exclusion criteria included personal history of previous CRC and age over 84 years. An interview was completed for 66% (698 men and 494 women) of the eligible cases. The main reasons for nonparticipation were death before contact (15%), refusal (11%), severe illness (5%), and inability to locate (3%).

Controls were randomly selected among the participants in an ongoing health survey conducted by the Hawaii State Department of Health in a 2% random sample of state households. Because this survey is mandated by law, the refusal rate is low. One control was matched to each case on sex, race, and age (control's age at interview within $\pm$ 2.5 years of the case's age at diagnosis). The overall participation rate for the controls was 71%. Reasons for nonparticipation included refusal (18%), inability to locate (5%), serious illness (3%), and death (3%).

Interviews were conducted in person, most often at the subjects' homes, by trained interviewers who could not be blinded to the case-control status of the subjects but who were unaware of the specific hypotheses under study. The questionnaire took an average of 2 h to administer and included: (*a*) detailed demographic information, such as the race of each grandparent; (*b*) a quantitative food frequency questionnaire; (*c*) a lifetime history of tobacco and alcohol use; (*d*) a history of recreational sports activities since age 18; (*e*) a lifetime history of occupational physical activity; (*f*) a personal history of various relevant medical conditions; (*g*) a family history of cancer, including CRC; and (*h*) information on height and weight.

The food frequency questionnaire used in this study (6) had been validated previously in our population (7). Frequencies and amounts consumed were sought for more than 282 food items. The reference period for the diet questionnaire was the 3-year period before the onset of symptoms for the cases and the 3-year period before interview for the controls. The particular foods included in the questionnaire were chosen based on 3-day food records collected from randomly selected individuals of the five main ethnic groups in Hawaii. The questionnaire was designed to capture the complete diet, including total caloric intake. Colored photographs of most food items, showing three different portion sizes, as well as measuring cups and spoons, were used during the interview to facilitate quantification of intakes. Subjects were also questioned about the brand and dose of any vitamin and mineral supplements taken for a minimum of 6 months during the reference period. The food composition data were primarily based on the United States Department of Agriculture's nutrient database (8) and were supplemented with data from other research and commercial publications (9–11). Nutrient content information for supplements was obtained from the manufacturers.

For all of the analyses, family history of CRC was defined as reporting at least one first-degree relative (parent or sibling) with the disease. Nutrient intakes were adjusted for calories by the method of residuals (12). The main effects of family history and other risk factors, such as daily nutrient and food intakes, and the interactions with family history were modeled using conditional logistic regression (13) with adjustment for relevant covariates. Interaction is defined here to be any significant deviation from the joint effect predicted from the logistic regression (*i.e.,* multiplicative interaction) and was tested by a likelihood ratio test comparing the model with interaction terms and a model containing only the main effects; $P < 0.10$ was used for statistical significance because of the low power of this test for interaction. Strata were defined to be the age- and race-matched case-control pairs. Separate models were created for men and women. First, the interactions with lifestyle variables were modeled by five dummy variables representing the upper two tertiles of exposure for those with no family history and all of the tertiles for those with family history. The group in the lowest tertile of exposure and with no family history was taken as the reference group. Tertile cutpoints were sex-specific and based on data from the controls. ORs and 95% CIs were computed for the six risk groups by exponentiating the β coefficients and their CIs, assuming normality.

Next, a stepwise logistic regression was performed to determine which interactions with family history were independently important. Family history and all of the main effects found to be related to risk in previous analyses (calories, beef, eggs, calcium, NSP from vegetables, ethanol, pack-years, Quetelet index 5 years ago, and lifetime recreational physical activity) were forced into the model, whereas other main effects (other variables in Table 1 and polyunsaturated fat) and all of the possible interaction terms between family history and lifestyle variables competed for inclusion. Because no threshold effects were observed for the lifestyle exposures, they were entered as continuous variables to improve the power for detecting associations. For males, interactions between family history and two lifestyle variables were significant. For females, no interactions entered the model. We denote x as the indicator variable for family history, z as the first lifestyle variable interacting with family history, y as the second such variable, and w_1–w_m as the other lifestyle risk factors. Then, the final model for men can be represented as:

$$\text{logit}(d) = \alpha + \beta x + \gamma z + \phi y + \sum \varphi_j w_j + \nu(x*z) + \varsigma(x*y)$$

and for women as

$$\text{logit}(d) = \alpha + \beta x + \gamma z + \phi y + \sum \varphi_j w_j$$

The final models are presented in two ways:

(*a*) the magnitude of interactions in the male model was investigated by representing z and y by dummy variables indicating tertile membership (whereas all of the other lifestyle variables were continuous) and jointly computing the OR for each combination of family history and lifestyle exposure for these variables (Table 3). Interaction with family history in the male model was tested for significance by a likelihood ratio test that compared the model with interaction terms and a model containing only the main effects; the P for this four-degrees-of-freedom test is given in Table 3;

(*b*) all of the lifestyle risk factors (as continuous variables), along with family history, were entered in the sex-specific final models. Interaction in this male model was tested with a two-degree-of-freedom likelihood ratio test, the P of which is given in Table 4. We also investigated the joint effects of the variables in these final (continuous) models using a summary variable for "healthy lifestyle" based on the regression coefficient weighted linear combination of lifestyle factors. For illustrative purposes, a healthy lifestyle was defined as being at the 33rd percentile of exposure for all of the direct risk factors and at the 67th percentile for all of the protective risk factors. Similarly, an unhealthy lifestyle was defined as being at the 67th percentile for all of the direct risk factors and at the 33rd percentile for all of the protective risk factors. ORs were computed for the 2 $\times$

Table 1 Distribution of cases and controls by sex and family history of CRC among parents or siblings

Sex and family history	Japanese		Caucasian		Filipino		Hawaiian		Chinese		Total	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Male												
No	289	323	156	166	66	70	46	48	46	48	603	655
Yes	58	24	24	14	4	0	6	4	3	1	95	43
Female												
No	203	232	100	106	48	50	36	38	33	36	420	462
Yes	41	12	16	10	2	0	6	4	9	6	74	32

2 combinations of family history (yes *versus* no) and lifestyle (healthy *versus* unhealthy), taking those with no family history and a healthy lifestyle as the reference group (Table 4). As an example, suppose the final model for males is

$$\text{logit}(d) = \alpha + \beta x + \gamma z + \varphi w + \nu(x{*}z)$$

where z is an adverse risk factor and w is a protective risk factor. The OR for those with family history and an unhealthy lifestyle would be

$$\exp(\beta + \gamma(z_{67} - z_{33}) + \varphi(w_{33} - w_{67}) + \nu(z_{67} - z_{33}))$$

where x_p is the p-th percentile of x.

Finally, using the final models and the definition of healthy and unhealthy lifestyle, attributable risk (*AR*) was computed based on the adjusted OR from the logistic model and the covariate distribution of the cases, as proposed by Bruzzi *et al.* (14). Specifically,

$$AR = 1 - \frac{1}{N}\sum_i \frac{1}{r_i}$$

where N is the number of cases and r_i is the relative risk for case i. This calculation assumes that the cases represent a random sample of all of the CRC patients on Oahu, which is reasonable given the population-based design of the study. AR calculated this way varies between 0 and 100%. It is of interest to investigate the risk reduction possible if the lifestyle factors were changed to healthy levels (*i.e.*, the low-risk tertile for each lifestyle factor). To compute this, the relative risk for case i is defined as $r_i = \exp(B' Y_i)$, where B is the coefficient vector from the logistic model and Y_i is set equal to the desired amount of change for individual i, *i.e.*, the difference between the actual level and the healthy level. If the individual's level is already healthy ($\leq$ the lowest tertile for adverse risk factors or $\geq$ the highest tertile for protective risk factors), that covariate is set to zero.

Results

Fifty percent of the subjects were of Japanese ancestry, whereas 25% were Caucasian, 10% Filipino, 8% Hawaiian and 8% Chinese. The mean age for cases was 66 years, compared with 64 years for controls. Cases were more often male (59%) than female but in a similar proportion to CRC patients in our population. In close agreement with past studies (15–19), 14% (169) of the cases and 6% (75) of the controls reported a family history of CRC among their parents or siblings. Table 1 presents the sex and ethnic distribution of cases and controls with such a family history.

Table 2 presents the adjusted ORs and 95% CIs for the two-way interactions of family history and several lifestyle variables found to be associated with CRC in previous analyses of this study (5, 20, 21). Significant interactions ($P \leq 0.1$) with family history were observed for: (*a*) P:S ratio and intakes of beef and chicken without skin in males; (*b*) processed meat, total calcium, and methionine intakes in females; and (*c*) saturated fat in both sexes. There was no association with beef intake in females irrespective of family history. A particularly strong association was found with ethanol intake in men reporting a family history, with an OR for the upper tertile of 5.7 (95% CI, 2.4–13.2), although the P for interaction was not significant.

Recognizing that some of the interactions noted above may not be independent from each other, we performed a stepwise logistic regression with all of the possible interactions between family history and the lifestyle variables competing for entry into the model. In men, only the interaction terms for beef and ethanol were retained. The interactions of beef and ethanol (as continuous variables) with family history were highly significant ($P = 0.001$ for the two-degrees-of-freedom test). The main effect for saturated fat was also entered in the male model. In women, no interaction terms entered the stepwise regression, but the main effect for methionine did. The adjusted ORs for the interactions in men, modeled as dummy variables depicting tertiles, are presented in Table 3. (The interaction terms are significant here at $P = 0.03$ for this four-degrees-of-freedom test.) In men, the associations for beef and ethanol with CRC were much stronger in individuals with a family history, the OR for beef reaching 10.8 (95% CI, 4.2–27.6) for the upper tertile of intake, compared with those in the first tertile and without a family history. The corresponding OR for ethanol was 7.5 (CI, 3.1–18.2). Stratification on age at diagnosis (<65, ≥ 65) or subsite of the large bowel (right colon, left colon, rectum) did not suggest that these interactions were stronger for a particular age group or subsite, although the power was limited for these subset analyses. However, consistent with the stronger overall association of family history with CRC in Japanese compared with Caucasians in this study (2), the interactions with meat and alcohol were stronger for Japanese men ($P = 0.16$) than for Caucasian men ($P = 0.52$).

Finally, overall ORs were computed from the final adjusted model (with all of the covariates entered continuously) for an increment of all of the lifestyle variables equal to the intertertile range of exposure in subjects with and without family history (Table 4). For men with a healthy lifestyle (*i.e.*, with each environmental exposure variable set to the low-risk tertile), family history was not associated with risk. In contrast, the combination of an unhealthy lifestyle (*i.e.*, when each variable was set to the high-risk tertile) and a positive family history was particularly detrimental with an OR of 11.7 (95% CI, 5.8–23.9), compared with no family history and a healthy lifestyle. In women, the main effects of family history and lifestyle were both statistically significant and of comparable magnitude (there was no interaction term in the female model).

Table 2 ORs[a] (95% CIs) for two-way interactions of family history with various lifestyle variables on the risk of CRC

Lifestyle variable and family history	Males (698 case-control pairs)			Females (494 case-control pairs)		
	T_1[b] (low)	T_2	T_3 (high)	T_1 (low)	T_2	T_3 (high)
	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Total calories						
No	1.0[c]	1.2 (0.9–1.7)	1.8 (1.3–2.6)	1.0[c]	1.1 (0.8–1.7)	1.2 (0.8–1.8)
Yes[d]	2.0 (0.8–4.6)	4.1 (1.7–9.6)	4.1 (2.0–8.6)	2.5 (1.0–5.7)	4.4 (1.5–12.9)	2.9 (1.2–7.0)
		$P^e = 0.66$			$P = 0.78$	
Calories from fat						
No	1.0	1.0 (0.7–1.4)	1.6 (1.1–2.4)	1.0	1.0 (0.7–1.5)	0.9 (0.6–1.5)
Yes	2.5 (1.0–6.2)	2.8 (1.3–6.0)	3.7 (1.7–7.8)	3.6 (1.1–11.0)	2.7 (1.2–6.0)	2.0 (0.7–5.5)
		$P = 0.53$			$P = 0.89$	
Calories from other sources						
No	1.0	1.1 (0.8–1.6)	1.8 (1.2–2.7)	1.0	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Yes	2.0 (0.8–4.8)	2.9 (1.4–6.1)	4.9 (2.2–10.8)	2.5 (1.1–6.1)	3.2 (1.1–8.7)	2.3 (0.9–5.6)
		$P = 0.85$			$P = 0.88$	
Saturated fat						
No	1.0	0.9 (0.7–1.3)	1.2 (0.8–1.7)	1.0	1.0 (0.7–1.5)	1.6 (1.0–2.4)
Yes	3.0 (1.3–6.7)	4.1 (1.7–9.9)	1.5 (0.7–3.3)	3.8 (1.5–9.4)	4.8 (1.7–13.6)	1.8 (0.7–4.6)
		$P = 0.08$			$P = 0.06$	
P:S ratio						
No	1.0	1.1 (0.8–1.6)	0.6 (0.4–1.0)	1.0	0.7 (0.5–1.1)	0.6 (0.4–0.9)
Yes	1.3 (0.6–2.9)	2.7 (1.3–5.6)	3.0 (1.3–6.9)	1.6 (0.7–6.0)	3.1 (1.2–7.7)	1.5 (0.6–3.9)
		$P = 0.10$			$P = 0.26$	
Beef[f]						
No	1.0	1.1 (0.8–1.6)	1.4 (0.9–2.1)	1.0	0.7 (0.5–1.1)	0.9 (0.6–1.4)
Yes	1.3 (0.5–3.2)	2.3 (1.1–4.8)	7.6 (3.0–19.0)	2.8 (1.1–7.1)	1.9 (0.8–4.6)	2.6 (1.0–6.8)
		$P = 0.07$			$P = 0.99$	
Processed meats						
No	1.0	1.4 (1.0–2.0)	1.8 (1.2–2.7)	1.0	1.0 (0.7–1.5)	1.3 (0.8–2.1)
Yes	2.8 (1.0–7.7)	3.3 (1.6–6.0)	4.5 (2.1–9.4)	4.7 (1.9–11.2)	3.8 (1.1–13.4)	1.5 (0.6–3.7)
		$P = 0.96$			$P = 0.05$	
Eggs						
No	1.0	1.7 (1.2–2.5)	2.4 (1.6–3.7)	1.0	1.3 (0.8–2.0)	2.2 (1.4–3.5)
Yes	3.7 (1.5–9.0)	3.1 (1.5–6.5)	7.3 (3.2–17.0)	5.3 (1.9–15.1)	3.8 (1.4–10.4)	3.2 (1.4–7.3)
		$P = 0.39$			$P = 0.12$	
Chicken without skin						
No	1.0	0.9 (0.7–1.3)	0.7 (0.5–0.9)	1.0	0.8 (0.6–1.2)	0.6 (0.4–0.9)
Yes	2.6 (1.2–5.9)	1.2 (0.6–2.5)	3.3 (1.4–7.7)	1.6 (0.7–3.8)	2.3 (0.9–5.5)	3.1 (1.1–9.0)
		$P = 0.06$			$P = 0.21$	
Margarine						
No	1.0	1.1 (0.8–1.6)	1.4 (0.9–2.0)	1.0	1.2 (0.8–1.7)	1.9 (1.3–3.0)
Yes	2.2 (0.9–5.3)	3.1 (1.6–6.2)	3.1 (1.3–2.6)	3.6 (1.3–10.0)	3.6 (1.4–9.6)	3.9 (1.6–9.4)
		$P = 0.90$			$P = 0.62$	
Total calcium[g]						
No	1.0	0.8 (0.6–1.2)	0.7 (0.5–1.0)	1.0	1.2 (0.8–1.7)	1.1 (0.7–1.7)
Yes	2.5 (1.1–5.5)	2.7 (1.2–6.0)	1.4 (0.6–3.0)	6.0 (2.2–16.2)	3.2 (1.2–8.3)	1.2 (0.4–3.2)
		$P = 0.73$			$P = 0.04$	
NSP						
No	1.0	0.8 (0.6–1.1)	0.6 (0.4–0.9)	1.0	0.8 (0.6–1.2)	0.7 (0.5–1.1)
Yes	3.2 (1.5–7.0)	1.4 (0.7–2.9)	1.8 (0.8–4.2)	2.8 (1.1–7.5)	1.6 (0.7–3.6)	2.4 (0.9–6.4)
		$P = 0.46$			$P = 0.65$	
Total carotenoids						
No	1.0	0.8 (0.6–1.1)	0.8 (0.5–1.1)	1.0	0.9 (0.6–1.4)	1.0 (0.6–1.6)
Yes	2.3 (1.1–4.9)	2.4 (1.1–5.4)	1.9 (0.8–4.2)	2.2 (1.0–5.0)	3.8 (1.5–9.5)	1.8 (0.6–5.0)
		$P = 0.88$			$P = 0.44$	
Methionine						
No	1.0	0.8 (0.6–1.2)	0.8 (0.5–1.1)	1.0	0.8 (0.5–1.2)	0.7 (0.4–1.0)
Yes	1.6 (0.8–3.3)	2.2 (1.0–4.8)	3.5 (1.5–8.3)	6.3 (2.4–16.4)	1.0 (0.4–2.6)	1.0 (0.4–2.9)
		$P = 0.15$			$P = 0.04$	
Legumes and soy						
No	1.0	0.9 (0.6–1.2)	0.9 (0.6–1.3)	1.0	0.9 (0.6–1.4)	0.8 (0.5–1.2)
Yes	3.1 (1.2–7.8)	1.5 (0.7–3.4)	2.6 (1.2–5.4)	2.4 (0.9–6.4)	2.0 (0.9–4.8)	2.4 (0.9–6.7)
		$P = 0.56$			$P = 0.86$	
Total vegetables						
No	1.0	0.7 (0.5–1.0)	0.6 (0.4–0.9)	1.0	0.7 (0.5–1.1)	0.6 (0.4–0.9)
Yes	1.3 (0.6–2.8)	2.0 (1.0–4.1)	2.7 (1.1–6.9)	2.2 (1.0–4.7)	1.6 (0.6–4.4)	2.3 (0.8–6.6)
		$P = 0.13$			$P = 0.61$	

Table 2 Continued

Lifestyle variable and family history	Males (698 case-control pairs)			Females (494 case-control pairs)		
	T_1[b] (low)	T_2	T_3 (high)	T_1 (low)	T_2	T_3 (high)
	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Broccoli						
No	1.0	0.8 (0.5–1.1)	0.7 (0.5–1.0)	1.0	1.1 (0.7–1.6)	0.7 (0.4–1.0)
Yes	1.6 (0.8–3.4)	1.9 (0.9–4.3)	3.2 (1.3–7.7)	1.9 (0.8–4.4)	2.2 (0.9–5.6)	3.4 (1.2–9.4)
		$P = 0.22$			$P = 0.25$	
Ethanol						
No	1.0	1.0 (0.7–1.4)	1.2 (0.9–1.7)	1.0	0.9 (0.6–1.4)	1.3 (0.9–2.0)
Yes	1.7 (0.8–3.5)	2.1 (0.9–5.3)	5.7 (2.4–13.2)	2.8 (1.0–7.4)	3.2 (1.3–8.0)	2.7 (1.0–6.9)
		$P = 0.18$			$P = 0.71$	
Pack-years						
No	1.0	1.0 (0.7–1.4)	1.3 (0.9–1.9)	1.0	1.0 (0.6–1.7)	1.4 (0.9–2.1)
Yes	1.5 (0.7–3.5)	3.3 (1.6–7.0)	3.6 (1.6–7.8)	2.7 (1.4–5.3)	2.4 (0.8–7.7)	3.1 (0.9–11.0)
		$P = 0.37$			$P = 0.96$	
Lifetime recreational physical activity						
No	1.0	0.7 (0.5–1.0)	0.6 (0.4–0.8)	1.0	0.7 (0.4–1.0)	0.7 (0.5–1.1)
Yes	1.5 (0.7–3.3)	2.6 (0.6–3.3)	2.6 (1.2–5.5)	2.2 (0.9–5.3)	2.3 (0.8–6.7)	2.1 (0.9–4.8)
		$P = 0.17$			$P = 0.81$	
Quetelet index 5 years ago						
No	1.0	1.4 (1.0–2.0)	2.2 (1.5–3.1)	1.0	1.2 (0.8–1.8)	1.3 (0.8–1.9)
Yes	3.3 (1.5–7.2)	4.3 (1.8–10.0)	3.6 (1.7–7.6)	4.8 (1.5–15.1)	3.6 (1.5–8.4)	1.7 (0.7–4.6)
		$P = 0.38$			$P = 0.18$	

[a] Adjusted by conditional logistic regression for age, alcoholic drinks/week (except ethanol model), pack-years of cigarette smoking (except pack-years model), lifetime recreational physical activity (except physical activity model), Quetelet index 5 years ago (except Quetelet index model), dietary fiber (except NSP and NSP from vegetables models), calcium intake (except total calcium model), egg intake (except calorie variables, saturated fat, eggs, red meat, processed meats, P:S ratio, and margarine models), and total calories (except calorie variable models). Calories from fat and calories from other sources were additionally adjusted for each other. All of the nutrients were adjusted for calories by the method of residuals (12).

[b] T_1, tertile 1; T_2, tertile 2; T_3, tertile 3. The intertertile ranges (33rd–67th percentile) for daily intakes and the other variables were as follows: calories (kcal), males, 1,833–2,510, females, 1,403–1,951; calories from fat (kcal), males, 529–816, females, 415–658; calories from other sources (kcal), males 1,269–1,701, females, 995–1,339; saturated fat (g), males, 19.7–25.5, females, 14.7–18.3; P:S ratio, males, 0.87–1.21; females, 0.96–1.32; beef (g), males, 13.8–32.3, females, 11.9–25.2; eggs (g), males, 8.5–22.0, females, 5.6–14.6; chicken without skin (g), males, 2.6–13.2, females, 3.3–13.1; margarine (g), males, 2.1–5.7, females, 1.7–5.0; total calcium (mg), males, 553–907, females, 521–1,055; NSP (g), males, 13.3–20.1, females, 13.0–17.5; total carotenoids (μg), males, 7,051–10,576, females, 6,769–10,530; methionine (g), males, 1.7–2.1, females, 1.3–1.6; legumes and soy (g), males, 15.2–38.6; females, 11.7–33.6; total vegetables (g), males, 149–245, females, 157–242; broccoli (g), males, 3.9–12.3, females, 5.3–15.8; ethanol (g), males, 0.4–8.7, females, 0.0–0.13; pack-years, males 0.4–31.5; females, 0–16; lifetime recreational physical activity (h), males, 1,152–7,632, females, 0–1,152; Quetelet index 5 years ago (kg/m^2), males, 23.0–25.4, females, 21.3–24.6.

[c] Reference category.

[d] Ninety male cases and 42 male controls reported a family history of CRC among parents or siblings. The corresponding figures for females were 72 and 31. Seven cases and two controls with family history had missing values for covariates and were excluded from this analysis.

[e] *P*s were computed from the likelihood ratio test comparing the model with interaction terms and a model with only main effects.

[f] All types, except fat-trimmed.

[g] Calcium from foods and supplements.

Because lifestyle is modifiable, we computed the AR for lifestyle in the final models, in which all of the lifestyle variables were compared with the "healthy" tertile values. Because all of the lifestyle exposures were required to be at the lower-risk tertile, our definition of a healthy lifestyle is somewhat extreme and is only meant to be illustrative of the contribution of lifestyle to risk. For men, the AR for lifestyle was 74.1% among those with no family history and 90.6% among those with a family history. For women, the AR for lifestyle was 70.5% and did not vary by family history. As expected, the ARs for beef, ethanol, and both factors combined varied greatly depending on family history in men (1.1, 19.0, and 19.8%, respectively, for men without family history; and 51.1, 44.7, and 74.2%, respectively, for men with a positive family history). For women, the ARs for these dietary variables were 4.4, 5.3, and 9.5%, respectively. No single variable for men without family history or for women had an AR greater than 21%.

Discussion

In this population-based case-control study of colorectal adenocarcinoma, we observed several interactions between lifestyle and first-degree family history of CRC. In males (after adjustment for other covariates), beef and alcohol intakes showed strong interactions with family history in increasing the risk of CRC. By using a summary measure of lifestyle, family history was not found to be associated with CRC risk among men who were only moderately exposed to environmental risk factors, *i.e.*, who were at the lower-risk tertile for all of the lifestyle variables associated with the disease. In contrast, both a high exposure to lifestyle risk factors (*i.e.*, at the upper-risk tertile for all of the lifestyle variables) and a positive family history increased CRC risk markedly (almost 12-fold). Following such an "unhealthy" lifestyle was also found to increase CRC risk significantly (almost 5-fold) in the absence of any family history. No family history-lifestyle interactions were detected in women after adjustment for all of the important main effects. In this sex, both an unhealthy lifestyle and a positive family history significantly increased CRC risk.

Most past studies have focused on individuals with no obvious familial predisposition and have identified a number of potentially modifiable risk factors for colon cancer, including (*a*) high fat, high red meat, and high ethanol intakes; (*b*) low fiber and low vegetable intakes; (*c*) smoking; (*d*) physical

Table 3 ORs[a] (95% CI) for two-way interactions of family history with red meat and ethanol intake on the risk of CRC in men

Variable and family history	T_1[b] (low)	T_2	T_3 (high)	*P* for interaction
Beef				
No	1.0[c]	1.0 (0.7–1.5)	1.5 (1.0–2.3)	
Yes	1.4 (0.6–3.4)	2.6 (1.2–5.6)	10.8 (4.2–27.6)	
				$P = 0.03$[d]
Ethanol				
No	1.0[c]	1.0 (0.7–1.4)	1.4 (1.0–1.9)	
Yes	2.5 (1.1–5.7)	2.0 (0.9–4.2)	7.5 (3.1–18.2)	

[a] Adjusted by conditional logistic regression for calories, saturated fat, eggs, calcium, NSP from vegetables, pack-years, lifetime recreational physical activity, Quetelet index 5 years ago, and the variables in the table.
[b] T_1, tertile 1; T_2, tertile 2; T_3, tertile 3.
[c] Reference category.
[d] *P* for likelihood ratio test between the model with both sets of interaction variables and the main effect model (a four-degree-of-freedom test).

Table 4 ORs[a] (95% CI) for interaction between family history and a summary variable for lifestyle risk factors on CRC risk

Family history	Lifestyle[b]	Male	Female
No	Healthy	1.0[c]	1.0[c]
No	Unhealthy	4.8 (3.2–7.2)	3.1 (1.9–5.2)
Yes	Healthy	0.7 (0.3–1.8)	2.6 (1.6–4.3)
Yes	Unhealthy	11.7 (5.8–23.9)	8.3 (4.1–17.0)
	P for interaction[d]	0.001	NA[e]

[a] Estimated by conditional logistic regression.
[b] For the low risk (healthy) or high risk (unhealthy) lifestyle category, the lifestyle summary variable took either the value of the 33rd or the 67th percentile for the following continuous variables: calories, saturated fat (males only), beef, eggs, calcium, NSP from vegetables, ethanol, pack-years, Quetelet Index 5 years ago, lifetime recreational physical activity, methionine (females only), family history × beef (males only), family history × ethanol (males only). The intertertile ranges for the main effect variables are given in Table 2.
[c] Reference category.
[d] *P* for interactions in final model comparing the model with all of the variables listed in footnote *b* with one with only the main effects terms.
[e] NA, no interaction terms were included in the final model for females.

inactivity; and (*e*) obesity (22). The present study in Hawaii confirms these associations (5, 20, 21) but also suggests that lowering exposure to these lifestyle risk factors may achieve a major reduction in the incidence of CRC (a 70% reduction if exposures are all decreased to the lower-risk tertile level). Because no single risk factor had a particularly high AR, a comprehensive approach to lifestyle modification seems most promising as a general recommendation. In contrast, for the group of men with a family history, our data predicted that an equally strong risk reduction might be obtained by focusing only on lowering beef and ethanol intakes, a change that may be more easily achieved.

We are aware of only one previous report on lifestyle risk factors for CRC in individuals with a family history of the disease. A hospital-based case-control study by Fernandez *et al.* (23) in northern Italy assessed risk factors for CRC among individuals with a first-degree family history of the disease and found similar risk factors as for individuals without a family history. However, the strengths of these associations were not compared between familial and nonfamilial presentations of the disease.

To date, the numbers of individuals who have been unequivocally characterized as genetically susceptible (*e.g.*, because they carry an *APC* mutation or a defective DNA mismatch repair gene) are too limited to allow the investigation of possible interactions of genetic predisposition and environmental risk factors. Therefore, we have used family history as a proxy for genetic susceptibility in this study. Admittedly, family history is an imperfect surrogate for genetic predisposition. Familial clustering may not always be observed (*e.g.*, because of small families, late age of onset, or limited penetrance) or may merely result from shared environmental exposures. Although lifestyle is expected to correlate somewhat among adult relatives, there are only limited and inconsistent data documenting the extent of this correlation (24, 25). Because the present data did not allow us to separate the contributions of genetic susceptibility and lifestyle to familial aggregation, they should be considered as exploratory. Nevertheless, there is other evidence for a role of environmental risk factors in the development of CRC in genetically predisposed individuals.

With regard to the rare but highly penetrant inherited syndromes, a role for environmental factors in HNPCC would be consistent with the variation in tumor spectrum noted for this syndrome over time and between countries. A recent update on the original HNPCC family described by Warthin 100 years ago revealed that the excess of stomach and uterine cancers initially observed in this family had been replaced by a predominance of CRCs in recent generations (26), following the same (presumably environmentally-induced) secular trend as in the general population. Similarly, in Japan, an area of high stomach cancer incidence, members of HNPCC families develop gastric cancer more often than in the United States (27). Moreover, that environmental factors can alter the phenotypic expression of a familial form of CRC has been demonstrated in FAP patients by a small randomized intervention trial in which wheat fiber was shown to reduce the number of polyps (28).

In this study, we did not seek to collect all of the data needed to reliably characterize patients with HNPCC or FAP. However, in an attempt to subset such cases based solely on first-degree family history of CRC, we reran our analysis excluding subjects with two or more affected siblings or parents. The strengths of the interactions between family history and beef and alcohol were not substantially changed ($P = 0.04$ compared with $P = 0.03$ in Table 3), which suggests that highly penetrant genes may not play a predominant role in explaining our findings.

Another class of susceptibility genes, referred to as "low-penetrance genes," have been found to interact with environmental exposures to moderately increase or decrease CRC risk. These genes, because of their high frequency in the population, may play an important role in sporadic cases. Examples are (functional) polymorphisms in genes that are involved in the metabolic activation or detoxification of carcinogens or are part of the metabolic pathways of critical nutrients (29–31). It is notable that the lifestyle factors found to interact with family history in the present data—beef, which is the main type of red meat consumed in Hawaii, and ethanol—are dietary factors that have been incriminated in studies of genetic polymorphisms and CRC. Individuals who are expected, based on genotype for metabolic genes (such as *NAT2*, *CYP1A2*, and *CYP1A1*), to be particularly apt at enzymatically activating carcinogens present in cooked red meats have been found to be at increased risk for CRC (29, 30). Alcohol consumption has also been shown to negate the protective effect against CRC of a common polymorphism in the gene coding for 5,10-methylenetetrahydrofolate reductase (*MTHFR*), a polymorphism associated with higher intracellular levels of a folate metabolite (5,10-methylenetetrahydrofolate) which is required for normal DNA synthesis (31).

The different findings by gender in this study may be caused by chance or by lower exposure levels in females

(especially for ethanol) or may reflect underlying biological differences. Gender discrepancies in risk factors for CRC have been noted in several past studies (reviewed in Ref. 5). It is possible that purely constitutive factors may play a greater role in the etiology of CRC in women than men.

In this study, the history of CRC among parents and siblings was based on self-report. Studies have shown that the accuracy of such recall is reasonably good (32–34) and, most importantly, nondifferential between CRC patients and controls (33, 34). Thus, it does not appear likely that misclassification on family history because of recall error could explain our results. Similarly, recall bias on dietary exposures may have occurred but is expected from past studies to be limited (35). It is unclear how such a recall bias, and measurement error in general, could have spuriously created the observed interactions. Because of the exploratory nature of this study, a relatively large number of interactions were tested. As a result, some of the findings may have been due to chance and need replication in other datasets.

In summary, the present data suggest that family history increases the risk of sporadic CRC in men mainly through its interaction with lifestyle exposures, primarily a high beef and ethanol intake. They also suggest that the combination of a familial predisposition and an unhealthy lifestyle increases risk of CRC considerably. In the absence of a family history for the disease, an unhealthy lifestyle would also increase male CRC risk substantially. The study failed to detect such interactions in women. Estimation of population ARs suggested that a comprehensive reduction in exposure to lifestyle risk factors, and more specifically ethanol and beef for individuals with a familial predisposition for the disease, may have a large beneficial effect on CRC incidence.

Acknowledgments

We thank the Hawaii Tumor Registry, Castle Medical Center, Kaiser-Permanente Medical Center, Kuakini Medical Center, Queen's Medical Center, Straub Clinic and Hospital, St. Francis Medical Center, Tripler Medical Center, and Wahiawa General Hospital for their collaboration. The authors also thank Dr. John Grove for comments on the article and Aleli Vinoya for assistance with computer programming.

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