Energy restriction early in life and colon carcinoma risk: results of The Netherlands Cohort Study after 7.3 years of follow-up

Energy Restriction Early in Life and Colon Carcinoma Risk

Results of The Netherlands Cohort Study after 7.3 Years of Follow-Up

Miranda J. M. Dirx, Ph.D.[1]
Piet A. van den Brandt, Ph.D.[1]
R. Alexandra Goldbohm, Ph.D.[2]
L. H. Lumey, M.D., Ph.D.[3]

[1] Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

[2] Department of Epidemiology, TNO Nutrition and Food Research Institute, Zeist, The Netherlands.

[3] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York.

The Netherlands Cohort Study was supported by the Dutch Cancer Society.

Address for reprints: Miranda J.M. Dirx, Ph.D., Department of Epidemiology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands; Fax: 011-31-43-3884128; E-mail: MJM.Dirx@epid.unimaas.nl

Received January 3, 2002; revision received July 16, 2002; accepted August 7, 2002.

BACKGROUND. This study evaluated the effects of severe undernutrition during adolescence and subsequent colon carcinoma risk.

METHODS. The authors evaluated The Netherlands Cohort Study on Diet and Cancer (NLCS) among 62,573 women and 58,279 men aged 55–69 years at baseline. Information on diet and risk factors was collected by questionnaire in 1986. Additional information was collected concerning residence during the hunger winter (1944–1945), the World War II years (1940–1944), and father's employment status during the economic depression of 1932–1940, which were used as indicators of exposure. After 7.3 years of follow-up, 807 colon carcinoma cases (388 females and 419 males) were available for analysis.

RESULTS. Multivariate analysis showed that both men and women who had lived in a western city in 1944–1945 had a decreased colon carcinoma risk (men: relative risk [RR] = 0.85, 95% confidence interval [CI] = 0.62–1.16; women: RR = 0.80, 95%CI = 0.59–1.09). No association between colon carcinoma risk and urban versus rural residence was found during the war years (1940–1944). Having an unemployed father during the economic depression (1932–1940) was also associated with a small decrease in colon carcinoma risk for men (RR = 0.90, 95% CI =0.62–1.31) and women (RR = 0.75, 95%CI 0.49-1.14). In subgroup analyses, a decreased colon carcinoma risk for men and women who were in their adolescent growth spurt and living in a western city during the hunger winter of 1944–1945 was noted (men: RR = 0.72, 95% CI = 0.31–1.65; women: RR = 0.88, 95% CI = 0.40–1.96). No associations were statistically significant because of the limited study size.

CONCLUSIONS. In the current study, a weak inverse relation was found between energy restriction early in life and subsequent colon carcinoma risk for men and women. However, these findings need replication in a larger study. ***Cancer* 2003; 97:46–55.** © *2003 American Cancer Society.*

DOI 10.1002/cncr.11052

KEYWORDS: energy restriction, colon carcinoma, adolescence, famine, early diet.

Colon carcinoma is the fourth most common cancer worldwide. The incidence pattern is similar for men and women.[1] In The Netherlands, the colon carcinoma incidence is approximately 50 per 100,000 among women and 60 per 100,000 among men.[2] The hypothesis that nutritional habits in childhood or adolescence (particularly caloric intake) may be associated with increased colon carcinoma risk — possibly mediated by hormone levels, body size, or other components of energy balance — has attracted increased attention in recent years. Although animal models suggest that caloric restriction signif-

icantly reduces colon tumor risk,[3–8] the results from epidemiologic studies in humans are conflicting.[9,10]

Adult anthropometric measures (height, body mass index [BMI], and sitting height) often are used as a proxy to evaluate nutritional status during childhood and adolescence. Albanes et al.[11] demonstrated in their study of adult stature and colon carcinoma risk a stronger inverse association with the leg length component of stature than with sitting height. This finding agrees with early lifetime exposure hypotheses, because leg length is more sensitive to environmental influences during early life and adolescence than is sitting height.[12,13]

To investigate early dietary exposures in relation to subsequent cancer risk, proxy measures are generally needed, as no individual data are available on diet early in life. In The Netherlands, a substantial part of the population experienced a severe famine during World War II, the so-called "hunger" winter (1944–1945), especially in the western part of the country. This unique setting provided the opportunity to study the effects of severe undernutrition during adolescence on the risk of colon carcinoma later in life.[14–16] In addition, a period of chronically impaired nutrition existed in The Netherlands during the earlier years of World War II (1940–1944) and during the economic depression in the 1930s. As a consequence of the poor availability of food products in the cities, nutritional differences developed between cities and rural areas during the war years.[17,18]Food was in greater supply in the rural areas. Also, the ratio between the dietary nutrients was different for cities and rural areas. In the cities, carbohydrates contributed more to the total amount of energy (70 energy%) compared with the rural areas (65 energy%). The contribution of fat was also less in the cities compared with the rural areas (10 energy% vs. 15 energy%).

During the economic depression, the unemployment rate was high. Several surveys showed that unemployed families had little variation in their food pattern and their energy intake was lower compared with the energy intake of employed families.[19–21] The total amount of energy available for unemployed families compared with employed families was 3000 versus 3400 calories.[22] The daily menu of the unemployed familes consisted of boiled potatoes and some fat. In addition, the bread meals underwent changes, no longer including cheese, meat, and confectionary. The energy restriction during the economic depression, the war years, and the hunger winter is the subject of investigation in this study.

We evaluated the association between diet in adolescence and colon carcinoma risk in The Netherlands Cohort Study (NLCS) regarding diet and cancer. Men and women who experienced puberty during the economic depression, World War II, and the hunger winter were included in this prospective cohort study. We focused on the interaction with the age at which dietary restriction took place, particularly for men and women who were undergoing their adolescent growth spurt during this time. Our hypothesis is that energy restriction during childhood and adolescence will show a protective effect on colon carcinoma risk later in life.

MATERIALS AND METHODS

In September 1986, the NLCS was begun to investigate various lifestyle variables, dietary habits, and potential confounders of colon carcinoma. Also included were questions regarding the residences of the cohort members during their entire life, including the residence in the war years, the residence in the winter of 1944–1945, and father's employment status during the economic depression. A detailed description of the cohort study design has been reported elsewhere.[23] Briefly, the cohort included 62,573 women and 58,279 men who were 55–69 years old at the beginning of the study. The study population originated from 204 municipal population registries throughout the country. Baseline exposure data were collected by self-administered questionnaires. After the baseline exposure measurement, a subcohort was randomly sampled from the cohort and followed up biennially for vital status information. Incident cancer cases occurring in the entire cohort were identified by record linkage to cancer registries and a national pathology register. The method of record linkage has been described previously.[24]

The collected data from subcohort and colon carcinoma cases were key entered twice by a research assistant who was blinded with respect to subcohort/case status to minimize observer bias in coding and interpretation of the data. The current analysis is restricted to cancer incidence in the 7.3-year follow-up from September 1986 to December 1993. Completeness of cancer follow-up was estimated to exceed 96%. After these 7.3 years of follow-up, 807 colon carcinoma cases (388 females and 419 males) were available for analysis, after exclusion of all prevalent cancer cases and cases with in situ carcinoma. All prevalent cancer cases other than skin carcinoma were also excluded from the subcohort, with the result that 3346 subjects (1630 men and 1716 women) remained in this group. For data analysis, the case–cohort approach was used in which cases were derived from the entire cohort and the person-years at risk were estimated from the subcohort.

Assessment of Energy Restriction

The exposure variables have to adequately represent the energy restriction of the subjects in the cohort for the economic depression years (1932–1940), the war years (1940–1944), and the hunger winter (1944–1945). Individual food intake data of the cohort members in these periods were not available. Instead, we used proxy variables for the energy restriction in each of these periods. For the economic depression years (1932–1940), the occupation of the father was the best available proxy variable for energy restriction. Contemporary studies observed that having an unemployed father indicated that the family had less energy to consume and less variation in their food pattern compared with families with an employed father.[19–22] The exposure variable for the economic depression years was dichotomous: subjects whose father had a job and subjects whose father had no job. For the other two periods, the war period (1940–1944) and the hunger winter (1944–1945), the city of residence during these periods was used to approximate the exposure for energy restriction. Living in a city in 1942 (midpoint year 1940–1944) with more than 40,000 inhabitants was considered to be an indicator for energy restriction in the war period because of the documented nutritional differences between a city and a rural area. This exposure variable was dichotomous, cohort members living in a city in 1942 or living in a rural area in 1942.

With respect to the hunger winter, three categories were defined, i.e., subjects who lived in a western city, subjects who lived in a western rural area, and subjects who lived in a nonwestern part of The Netherlands. Living in a western city in 1944–1945 was considered to be an indicator for severe energy restriction. The definition of a famine city ($>$ 40,000 inhabitants) is based on the definition of a famine city according to the study of Stein et al.[25] The following western cities were determined as famine cities: Amsterdam, Rotterdam, The Hague, Utrecht, Zaandam, Hilversum, Amersfoort, Dordrecht, Vlaardingen/Schiedam, Delft, and Leiden.

To assess whether the timing at which dietary restriction took place modified the effect of energy restriction on the risk of colon carcinoma, rate ratios of colon carcinoma for energy restriction in each of the three periods were calculated within strata of the adolescent growth spurt (subgroup analyses). In these analyses, subjects were divided into subgroups depending on exposure to energy restriction before, during, or after the adolescent growth spurt. The analyses were conducted for men and women separately. For men, the adolescent growth spurt used in this study was defined as taking place between the ages of 12–15 years. For women, the adolescent growth spurt in this study was defined as 2 years before the reported age at menarche until 1 year after the reported age at menarche.[26] Because the exposure periods are age dependent and of varying duration, it was decided to restrict the relevant time span in the long exposure periods (i.e., 1932–1940 and 1940–1944) to the years in which the food situation was the worst. For the economic depression period, we selected the years 1933–1934 because the literature regarding this period showed a very poor food situation in the first years of the depression and some improvement in the later years. Therefore, only men and women with the adolescent growth spurt in 1933–1934 were included in the subgroup. For the war period, we selected the years 1942–1943 because they represent the worst years of the prefamine period.[17,18]

Data Analysis

The distributions of the exposure variables were compared for the colon carcinoma cases and subcohort members, for men and women separately. For the continuous covariates, i.e., age, BMI (kg/m^2), baseline alcohol and energy intake, vitamin C intake, beta carotene, height and weight, the mean values of these variables were compared between the exposure categories. Statistical significance of these associations was tested by *t* tests and analysis of variance. Significance of the association between categorical covariates — such as large bowel carcinoma in the family (yes/no), baseline physical activity ($<$ 30 minutes per day, 30–60 minutes per day, 60–90 minutes per day, $>$ 90 minutes per day), education (low, medium, high), meat consumption (less than once per week, one to four times a week, more than four times per week), and smoking (never/ever) — and the exposure categories was tested by chi-square test. Baseline recreational physical activity was used as the combination of the number of minutes spent per day on biking/walking, shopping, walking the dog and the number of hours spent per week on gardening/doing odd jobs, cycling/walking, and sport/gymnastics.

The association between exposure variables and covariates was studied in the subcohort. Covariates associated with colon carcinoma itself or with any of the exposure variables were considered to be potential confounders. In the multivariate analysis, adjustment was made for age, familial large bowel carcinoma, BMI, baseline alcohol and energy intake, recreational physical activity, and education.

Data were analyzed using the case–cohort approach.[27,28] The cases were derived from the entire cohort and the person-years at risk of the entire cohort were estimated from a random sample of 3500 people

TABLE 1
Distributions of the Food Restriction Exposure Variables for Colon Carcinoma Cases and Subcohort Members, Separately for Men and Women in The Netherlands Cohort Study (September 1986–December 1993)[a]

	Men[b]		Women[c]	
Exposure variables	Subcohort (%) (n = 1630)	Cases (%) (n = 419)	Subcohort (%) (n = 1716)	Cases (%) (n = 388)
Hunger Winter 1944–1945				
Non-West	794 (59.8)	209 (63.7)	899 (56.4)	217 (59.3)
Rural Western area	199 (15.0)	39 (11.9)	240 (15.1)	58 (15.9)
Western city	334 (25.2)	80 (24.4)	454 (28.5)	91 (24.8)
War years 1940–1944				
Rural area in 1942	576 (49.7)	131 (45.2)	598 (48.9)	162 (51.7)
City in 1942	582 (50.3)	159 (54.8)	624 (51.1)	151 (48.3)
Economic depression 1932–1940				
Father a job	1349 (87.8)	357 (89.0)	1418 (88.5)	324 (89.5)
Father no job	187 (12.2)	44 (11.0)	184 (11.5)	38 (10.5)

[a] Due to missing data, numbers may not add up to 1630, 419, 1716, and 388, respectively.
[b] Men (1630 subcohort members and 419 cases).
[c] Women (1716 subcohort members and 388 cases).

(subcohort). Incidence rate ratios (RR) and corresponding 95% confidence intervals (CI) for colon carcinoma were estimated using exponentially distributed failure time regression models from the Stata statistical package. In multivariate analyses, adjustment for covariates was performed. All analyses were carried out with Stata software.[29]

RESULTS

Table 1 shows the distributions of the exposure variables for colon carcinoma cases and subcohort members. During the hunger winter, there were proportionally more men and women from the case group living in the nonwestern region compared with the subcohort members. The distribution of women during the war years and the economic depression years was equal for cases and subcohort female members.

In the subcohort, men living in a western rural area in 1944–1945 were the tallest, had the highest energy intake at baseline, and the lowest BMI compared with men living in a western city in 1944–1945 and with men living in a nonwestern region. Men living in a western city in 1944–1945 were more educated than men living in a nonwestern region or a western rural area. Men who lived in a city in 1942 had a lower weight and BMI, a lower energy intake at baseline, and were more educated compared with men who lived in a rural area in 1942 (Table 2).

Table 3 shows that women who lived in a western city in 1944–1945 had a lower BMI and a lower energy intake at baseline, a higher intake of alcohol at baseline, and were more educated compared with women living in a western rural area or in a nonwestern region. Women who lived in a city in 1942 had a lower weight at age 20 years, had a higher alcohol intake, a lower energy intake at baseline, and were more educated compared with women who lived in a rural area in 1942. Women whose father had no job during the economic depression were younger, shorter, had a lower weight at age 20 years, had a lower energy intake at baseline, and were less educated compared with women whose father had a job during the depression years.

Table 4 shows the results of the age-adjusted and multivariate analyses in which adjustment was made for age, familial large bowel carcinoma, BMI, baseline alcohol and energy intake, education, and baseline recreational physical activity. The multivariate analyses showed a small but nonsignificant inverse relation between living in a western city in 1944–1945 and colon carcinoma risk for men and women separately. The combined analyses for men and women showed that men and women who lived in a western city had an RR of 0.81 (95%CI 0.65–1.01, P = 0.02) compared with men and women living in a nonwestern region (data not shown).

The RR for men living in a western City in 1944–1945 was 0.85 (95%CI 0.62–1.16) and for women, the RR was 0.80 (95%CI 0.59–1.09) compared with the reference category. Living in a city in 1942 was not related to colon carcinoma risk. Having a father without a job during the depression years showed a small but nonsignificant decrease in colon carcinoma risk, both for men and women.

TABLE 2
Means (Standard Deviations [SD]) and Distribution of Potential Confounders in the Male Subcohort by Exposure Category

	Hunger winter (1944–1945)			War years (1940–1944)		Economic depression (1932–1940)	
	Nonwest	Rural west	City west	Rural area	City	Father a job	Father no job
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	61.0 (4.2)	60.7 (4.2)	61.2 (4.4)	61.1 (4.2)	61.6 (4.2)	61.3 (4.2)	61.5 (4.3)
Height	176.1 (6.7)	178.9 (7.0)	177.0 (6.6)[a]	176.6 (7.0)	176.2 (6.7)	176.8 (6.7)	176.6 (7.4)
Weight	78.5 (9.7)	78.0 (9.7)	77.8 (9.5)	79.0 (9.9)	77.0 (9.0)[a]	78.2 (9.7)	77.9 (9.9)[a]
Weight at age 20 yrs	68.3 (8.1)	68.0 (9.2)	67.1 (8.1)	68.4 (8.1)	67.4 (8.6)	67.8 (8.3)	68.0 (9.8)
Body mass index (kg/m^2)	25.3 (2.7)	24.4 (2.6)	24.8 (2.6)[a]	25.3 (2.7)	24.8 (2.6)[a]	25.0 (2.6)	24.9 (2.8)
Alcohol intake 1986 (g/day)	14.8 (16.9)	14.0 (15.0)	13.8 (16.7)	13.7 (14.9)	13.8 (16.2)	14.7 (16.9)	13.4 (14.5)
Energy intake 1986 (kcal/day)	2181 (529)	2208 (514)	2090 (460)[a]	2192 (529)	2113 (485)[a]	2167 (514)	2116 (498)
Large bowel carcinoma in family (%)							
No	95.5	95.0	94.9	95.5	94.7	94.4	96.2
Yes	4.5	5.0	5.1	4.5	5.3	5.6	3.8
Education (%)							
Low	53.2	50.8	37.6[a]	31.5	43.3[a]	45.9	64.1[a]
Medium	30.9	32.2	38.7	58.3	40.3	36.0	23.4
High	15.9	17.0	23.7	10.2	16.4	18.1	12.5
Baseline physical activity (%)							
< 30 min/day	19.2	21.8	17.9	19.2	18.4	18.1	21.6
30–60 min/day	31.9	34.5	27.3	33.5	28.1	31.2	28.1
60–90 min/day	18.1	21.3	22.4	17.0	19.1	19.7	13.5
> 90 min/day	30.8	22.4	32.4	30.3	34.4	31.0	36.8

[a] Analysis of variance, *t* test, or chi-square test: $P < 0.05$.

Subgroup analyses were conducted to evaluate possible effects of the timing of energy restriction. As a consequence of the small number of cases in the "before growth spurt in the hunger winter" subgroup for women and the "before growth spurt in the war years" subgroup for men, the multivariate model did not converge. For these subgroups, we conducted an age-adjusted analysis. In our cohort, none of the men were exposed to the hunger winter before their growth spurt because all the men were older than 12 years at the time of the hunger winter.

Exposure to energy restriction during the adolescent growth spurt (Table 5) shows a nonsignificant decreased risk (RR = 0.72, 95% CI = 0.31–1.65) for men living in a western city compared with men living in a nonwestern city. A decreased risk (RR = 0.43, 95% CI = 0.14–1.33) was also seen for men living in a western rural area compared with men living in a onwestern area during the hunger winter. However, the number of cases is very small and the pattern is inconsistent across the different proxies for energy restriction and across the different subgroups.

Men who were exposed to the hunger winter after their growth spurt showed a decreased risk, both for men living in a western city or in a western rural area (RR = 0.87, RR = 0.77, respectively). Exposure during the adolescent growth spurt shows a small, but nonsignificant, decreased risk (RR = 0.88, 95% CI = 0.40–1.96) for women living in a western city during the hunger winter compared with women living in a nonwestern part of the country. For exposure during the war years, there was no difference in risk between women living in a city during their adolescent growth spurt and women living in a rural area. The RR for the women whose father had no job in 1933–1934 and who were in their growth spurt during the depression years showed a decrease in breast carcinoma risk (RR = 0.62, 95% CI = 0.29–1.31) that was not statistically significant (Table 6). Again, the number of cases is quite small.

DISCUSSION

This prospective cohort study found a nonsignificant and weak inverse relation between energy restriction during adolescence and the risk of colon carcinoma, after controlling for potential confounders. Compared with residents in the North and South of The Netherlands who served as controls with almost no exposure to energy restriction, the results showed a nonsignificant decreased colon carcinoma risk for men (RR = 0.85) and women (RR = 0.80) living in a western city. A nonsignificant decreased risk was observed (RR = 0.72) for men living in a western rural area in 1944–1945 and no difference was observed (RR = 1.09) for

TABLE 3
Means (Standard Deviations [SD]) and Distributions of Potential Confounders in the Female Subcohort by Exposure Category

	Hunger winter (1944–1945)			War years (1940–1944)		Economic depression (1932–1940)	
	Nonwest	Rural west	City west	Rural area	City	Father a job	Father no job
Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	61.4 (4.3)	61.4 (4.1)	61.7 (4.4)	61.5 (4.2)	61.6 (4.4)	61.4 (4.2)	61.1 (4.4)[a]
Height	165.4 (6.3)	165.1 (6.1)	165.2 (5.9)	165.3 (6.1)	164.9 (6.1)	165.2 (6.2)	163.9 (6.7)[a]
Weight	68.7 (10.4)	69.7 (10.6)	68.2 (10.0)	69.2 (10.3)	69.0 (10.3)	68.5 (10.1)	68.6 (11.0)
Weight at age 20 yrs	58.8 (8.0)	59.4 (7.6)	57.9 (7.6)	59.2 (7.9)	57.8 (7.3)[a]	58.7 (7.9)	56.9 (7.4)[a]
Body mass index (kg/m^2)	25.2 (3.6)	25.5 (3.6)	25.0 (3.4)[a]	25.3 (3.5)	25.4 (3.5)	25.1 (3.5)	25.5 (3.8)
Alcohol intake 1986 (g/day)	5.4 (9.3)	5.4 (8.3)	7.0 (10.9)[a]	4.7 (8.1)	6.4 (10.3)[a]	6.0 (9.8)	4.6 (8.2)
Energy intake 1986 (kcal/day)	1719 (419)	1712 (421)	1634 (379)[a]	1712 (424)	1652 (393)[a]	1695 (409)	1617 (428)[a]
Large bowel carcinoma in family (%)							
No	94.0	96.7	94.7	94.6	94.7	94.6	95.1
Yes	6.0	3.3	5.3	5.4	5.3	5.4	4.9
Education (%)							
Low	52.9	63.7	47.9[a]	72.0	49.3[a]	54.9	75.8[a]
Medium	30.1	27.4	41.6	22.9	41.4	35.8	21.5
High	7.0	8.9	10.5	5.1	9.3	9.3	2.7
Baseline physical activity (%)							
< 80 min/day	26.5	23.8	26.1	27.3	24.6	24.0	33.7
30–60 min/day	33.2	38.7	26.3	35.5	28.7	32.9	26.5
60–90 min/day	20.2	20.4	23.2	19.0	22.5	21.9	18.2
> 90 min/day	20.1	17.1	24.4	18.2	24.2	21.2	51.6

[a] Analysis of variance *t* test, or chi-square test: $P < 0.05$.

TABLE 4
Age-Adjusted and Multivariate Rate Ratios (RR) for Colon Carcinoma According to Three Time Periods of Energy Restriction in The Netherlands Cohort Study (1986–1993), Separately for Men and Women

	Men				Women			
Exposure	Cases	Person-yrs	RR[a] (95% CI)	RR[b] (95% CI)	Cases	Person-yrs	RR[a] (95% CI)	RR[b] (95% CI)
Hunger winter (1944–1945)								
Non-West	201	5115	1.00[c]	1.00[c]	193	5601	1.00[c]	1.00[c]
Rural West	35	1332	0.74 0.53–1.12	0.72 0.48–1.09	54	1507	1.01 0.81–1.57	1.09 0.77–1.55
City West	76	2158	0.90 0.74–1.23	0.85 0.62–1.16	81	2944	0.81 0.63–1.12	0.80 0.59–1.09
			P t = 0.23	*P* t = 0.14			*P* t = 0.13	*P* t = 0.15
War years (1940–1944)								
Rural area in 1942	123	3694	1.00[c]	1.00[c]	141	3641	1.00[c]	1.00[c]
City in 1942	151	3787	1.15 0.91–1.52	1.11 0.83–1.49	140	4092	0.88 0.73–1.12	0.88 0.67–1.19
Economic depression (1932–1940)								
Father had a job	340	8767	1.00[c]	1.00[c]	298	8985	1.00[c]	1.00[c]
Father had no job	41	1188	0.89 0.63–1.32	0.90 0.62–1.31	31	1108	0.86 0.64–1.21	0.75 0.49–1.14

CI: confidence interval; *P* t: *P* trend.

[a] Only age adjusted.

[b] Adjusted for age, familial large bowel carcinoma, body mass index, baseline alcohol and energy intake, education, and baseline recreational physical activity.

[c] Reference category.

women living in a western rural area. With respect to exposure during the remaining years of World War II (1940–1944), no differences in colon carcinoma risk were found for men and women who lived in a city (food-restricted area) in 1942 versus men and women who lived in a rural area in 1942. Having an unemployed father during the economic depression was associated with a small, but not significant, decrease in colon carcinoma risk for men (RR = 0.90) and women (RR = 0.75). Results of the subgroup analyses

TABLE 5
RR of Colon Carcinoma for Men Exposed to Energy Restriction before, during, and after Their Adolescent Growth Spurt (12–15 Years) in 1944–1945, 1942–1943, and 1933–1934 in The Netherlands Cohort Study (1986–1993)

	Before growth spurt				During growth spurt				After growth spurt			
Exposure	Cases	Person-yrs	RR[a]	95% CI	Cases	Person-yrs	RR[a]	95% CI	Cases	Person-yrs	RR[a]	95% CI
Hunger winter (1944–1945)												
Nonwest	No men exposed before their growth spurt				34	1258	1.0[b]		167	3857	1.0[b]	
Western rural area					4	359	0.43	0.14–1.33	31	973	0.77	0.50–1.22
Western city					10	535	0.72	0.31–1.65	66	1622	0.87	0.62–1.23
War years (1942–1943)												
Rural area in 1942	5	248	1.0[b,c]		23	1169	1.0[b]		95	2276	1.0[b]	
City in 1942	5	122	1.92	0.49–7.52	31	1216	1.28	0.66–2.47	115	2449	1.04	0.74–1.47
Economic depression (1933–1934)												
Father had a job	203	6356	1.0[b]		111	1945	1.0[b]		26	465	1.0[b]	
Father had no job	23	808	0.86	0.52–1.43	13	285	0.91	0.46–1.82	7	94	0.90	0.18–4.58

RR: relative rate; CI: confidence interval.
[a] Relative rate after adjustment for age, familial large bowel carcinoma, body mass index, baseline alcohol and energy intake, baseline recreational physical activity, and education.
[b] Reference category.
[c] Only age adjusted.

TABLE 6
RR of Colon Carcinoma for Women Exposed to Energy Restriction before, during, and after Their Adolescent Growth Spurt (2 years < Menarche < 1 Year) in 1944–1945, 1942–1943, and 1933–1934, in The Netherlands Cohort Study (1986–1993)

	Before growth spurt				During growth spurt				After growth spurt			
Exposure	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI	Cases	Person yrs	RR[a]	95% CI
Hunger winter 1944–1945												
Non-West	4	116	1.0[b,c]		28	1531	1.0[b]		161	3901	1.0[b]	
Western rural area	1	21	1.27	0.08–20.2	10	394	1.55	0.68–3.53	43	1091	1.00	0.68–1.49
Western city	0	65	1.63	3.76–7.03	13	736	0.88	0.40–1.96	65	2113	0.79	0.56–1.11
War years 1942–1943												
Rural area in 1942	7	297	1.0[b]		31	1141	1.0[b]		103	2173	1.0[b]	
City in 1942	8	409	0.25	0.03–2.02	35	1220	1.01	0.54–1.89	95	2445	0.84	0.59–1.20
Economic depression 1933–1934												
Father had a job	160	6179	1.0[b]		115	2236	1.0[b]		21	520	1.0[b]	
Father had no job	13	708	0.68	0.37–1.26	11	302	0.62	0.29–1.31	6	97	1.52	0.34–6.88

RR: relative rate; CI: confidence interval.
[a] Relative rate after adjustment for age, familial large bowel carcinoma, body mass index, baseline alcohol and energy intake, baseline recreational physical activity, and education.
[b] Reference category.
[c] Only age adjusted.

showed an inconsistent pattern across the different proxies for energy restriction, both for men and women.

There are limitations to NLCS. A factor that could have influenced the results is misclassification of food restriction exposure. For ethical and practical reasons, it is difficult to test the childhood nutrition hypothesis in western populations. Three proxy measures of energy restriction were used in this study: the father's employment status of the men and women during the economic depression years, residence during World War II (1940–1944), and residence during the hunger winter (1944–1945). Surveys have shown that energy intake was associated with father's employment status in 1932–1940,[19–21], that the food supply in the cities deteriorated much faster than in the rural area during 1940–1944,[17,18] and that starvation in 1944–1945 was confined mostly to western cities.14–16 However, we are aware that these ecologic measures are only a proxy measure of individual exposures. Other studies used the same proxy measure for energy restriction in the hunger winter and their results also indicated that the proxy measure for energy restriction in the hunger winter is reasonably adequate.[30,31] In a previous report

on energy restriction and breast carcinoma risk in the NLCS cohort, we asked the female subcohort members during follow-up if they really had experienced hunger during the winter of 1944–1945.[32] Of the women who reported severe hunger during the hunger winter, 80% lived in a western city during this winter. These results also indicated that the proxy measure for energy restriction in the hunger winter is reasonably adequate.[32] If misclassification is present, it will be nondifferential because of the prospective design of the cohort.

The potential for selection bias in the NLCS is low considering the high completeness of cancer follow-up. In addition, there were no reasons to assume that residual confounding was still present, because all known risk factors for colon carcinoma were measured and controlled for in multivariate analyses.

Energy intake is often related to a higher risk of colon carcinoma in case–control studies.[33–35] However, results from cohort studies that assessed total energy intake found a slight inverse association between total energy intake and risk of colon carcinoma.[36–39] These studies were not able to analyze the adolescent diet in relation to subsequent colon carcinoma risk later in life. In the NLCS cohort, no association was found between baseline energy intake and colon carcinoma risk.[40] To our knowledge, no other specific studies of early diet and colon carcinoma risk have been conducted.

Adult anthropometric measures (height, BMI, and sitting height) are often used as a proxy for nutritional status during childhood and adolescence. Russo et al.[41] conducted a case–control study to determine whether body size measurements at different ages were risk factors for colon carcinoma. Study subjects were asked to report their normal adult height and weight, weight at 30 years and at 50 years of age, and perceived body size at 12 years of age. Their study showed a positive association between BMI at various ages and colon carcinomarisk in men and women. Only in women was BMI at middle age unrelated to colon carcinoma risk. Other studies also found a positive association with excessive weight earlier in life, most notably at age 30 years.[42,43] Most of the studies found a positive association between colon carcinoma and weight in young adults.[42,44,45]

Giovannucci et al.[46] found a positive relation between adult height and colon carcinoma risk. Adult height might be a proxy of a positive energy balance during childhood and it is correlated with the total length of the colon. These observations agree with the association between body size and human cancer in the large population-based National Health and Nutrition Examination Survey (NHANES) study, suggesting that higher levels of energy intake in childhood increase the risk of later development of cancer. These findings provide further evidence that the unfavorable trends in the incidence of colon carcinoma may have its origin in early life.[47] In the NLCS cohort, we found a positive association between height and colon carcinoma risk for women, as well as positive associations between weight, BMI at age 20 years, and BMI change from age 20 years to baseline age (55–60 years) and colon carcinoma risk in men (Ariesen MJ, Dirx MJM, van den Brandt PA, et al.; unpublished data, 2002).

Energy intake, body mass, and physical activity are components of the energy balance. Slattery et al.[48] conducted a case–control study to determine how physical inactivity interacts with other components of energy balance (energy intake and body mass) to affect colon carcinoma risk. They concluded that those who had the most unfavorable energy balance, i.e., those who were physically inactive, had high energy intakes, and a large BMI, were at greatest colon carcinoma risk. Energy balance as a whole seems to be associated with risk of colon carcinoma.

Energy intake, body mass, and physical activity operate at different levels in the etiology of colon carcinoma, but the most plausible explanation that unifies the three has to involve metabolic profiles rather than local influences on colonic epithelium. McKeown-Eyssen[49] proposed that some factors that collectively characterize increased colon carcinoma risk (obesity and a western diet) may plausibly operate through influences on serum triglycerides and insulin resistance. Giovannucci[50] also reported that elevated blood insulin levels promote the growth of colon tumors. Bruce et al.[51] explained that an unfavorable energy balance, due to consumption of excess dietary energy or a sedentary lifestyle, may result in the development of insulin resistance with increased circulation levels of insulin, triglycerides, and nonesterified fatty acids. This occurs when the increased dietary energy increases intravascular energy as carbohydrates and lipids in the bloodstream.[52] The result is that all cells, including colonic epithelial cells, are exposed to increased concentrations of insulin and energy substrates. Increased proliferation and mutation may result from insulin resistance.[53,54]

The results of the current study demonstrated a weak inverse and nonsignificant relation between energy restriction early in life and subsequent colon carcinoma risk later in life. These findings did not appear to confirm or contradict the hypothesis. To study the interaction among physical activity, energy intake, and BMI, more cases are needed. Therefore, a longer follow-up is necessary for the NLCS cohort.

Future research should concentrate on the interaction among the components of energy balance (physical activity, body mass, and energy intake).

REFERENCES

1. Fund WCR. Food, nutrition and the prevention of cancer: a global perspective, Washington, DC: American Institute for Cancer Research, 1997.
2. Schouten LJ, De Rijke JM, Huveneers JAM, Jager JJ, Van den Brandt PA. Cancer incidence in mid and south Limburg, the Netherlands. Maastricht: Maastricht Cancer Registry, 2000.
3. Ross MH, Bras G. Lasting influence of early caloric restriction on prevalence of neoplasmsm in the rat. *J Natl Cancer Inst.* 1971;47:1095–1103.
4. Tannenbaum A. The genesis and growth of tumors, effects of a high fat diet. *Cancer Res.* 1942;2:468–475.
5. Kritchevsky D, Klurfeld DM. Influence of caloric intake on experimental carcinogenesis: a review. *Adv Exp Med Biol.* 1986;206:55–68.
6. Albanes D, Salbe AD, Levander OA, Taylor PR, Nixon DW, Winick M. The effect of early caloric restriction on colonic cellular growth in rats. *Nutr Cancer.* 1990;13:73–80.
7. Kritchevsky D, Klurfeld DM. Interaction of fiber and energy registration in experimental colon carcinogens. *Cancer Lett.* 1997;114:51–52.
8. Kritchevsky D. Colorectal cancer: the role of dietary fat and caloric restriction. *Mutat Res.* 1993;290:63–70.
9. Slattery ML, Caan BJ, Potter JD, et al. Dietary energy sources and colon cancer risk. *Am J Epidemiol.* 1997;145:199–210.
10. Giovannucci E, Goldin B. The role of fat, fatty acids, and total energy intake in the etiology of human colon cancer. *Am J Clin Nutr.* 1997;66(6 Suppl):1564s–1571s.
11. Albanes D, Jones DY, Schatzkin A, Micozzi MS, Taylor PR. Adult stature and risk of cancer. *Cancer Res.* 1988;48:1658–1662.
12. Gunnel DJ, Smith GD, Holly JMP, Frankel S. Leg length and risk of cancer in the Boyd Orr cohort. *Br Med J.* 1998;317:1350–1351.
13. Tanner JM, Hayashi T, Preece MA, Cameron N. Increase in length of leg relative to trunk in Japanese children and adults from 1957 to 1977: comparison with British and with Japanese Americans. *Ann Hum Biol.* 1982;9:411–423.
14. Burger GCE, Sandstead HR, Drummond J. Starvation in western Holland: 1945. *Lancet.* 1945;ii:282–283.
15. Burger GCE, Drummond JC, Sandstead HR. Malnutrition and starvation in Western Netherlands, September 1944-July 1945. The Hague: Hague General State Printing Office, 1948.
16. Burger GCE, Drummond JC, Sandstead HR. Appendices to malnutrition and starvation in Western Netherlands, September 1944- July 1945 (Part II). The Hague: Hague General Sate Printing Office, 1948.
17. Breunis J. The food supply. *Ann Am Acad Pol Soc Sci.* 1946;245:87–92.
18. Dols MJL, Van Arcken AJM. De voedselvoorziening in Nederland tijdens en onmiddelijk na den tweeden wereldoorlog 1940-1945 [Food supply during and after the Second World War 1940–1945 in the Netherlands]. *Voeding.* 1946;6:193–207.
19. Ten Bokkel Huinink SA. De voeding van de gezonde en zieke werkloozen [The nutrition of the healthy and ill unemployed people]. Thesis. Rotterdam: University of Rotterdam, 1936.
20. Kastein GW. De voeding van 343 werkloozengezinnen in Rotterdam en Schiedam in de wintermaanden van 1934-1935 [The nutrition of 343 unemployed families in Rotterdam and Schiedam in the winter of 1934–1935]. *Ned Tijdschr Geneeskd.* 1935;79:5583–5587.
21. Tromp MH. De voeding in het gezin van den werklooze [The nutrition of an unemployed family]. *Ned Tijdschr Geneeskd.* 1934;78:5388–5399.
22. den Hartog AP: Werklozen en hun voeding in de jaren 1930-1939 [Unemployed people and their nutrition in the depression years 1930-1939]. *Voeding.* 1983;44:92–98.
23. Van den Brandt PA, Goldbohm RA, Van 't Veer P, Volovics A, Hermus, RJJ, Sturmans F. A large scale prospective cohort study on diet and cancer in the Netherlands. *J Clin Epidemiol.* 1990;19:285–295.
24. Van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PMH. Development of a record linkage protocol for use in the Dutch cancer registry for epidemiological research. *Int J Epidemiol.* 1990;19:553–558.
25. Stein Z, Susser M, Saenger G, Marolla F. Famine and human development, the Dutch hunger winter of 1944-1945. New York: Oxford University Press, 1975.
26. Marshall WA, Tanner JM. Human growth, a comprehensive treatise. In: Falkner F, Tanner JM, eds. Puberty, 2nd ed. New York: Plenum Press, 1986:171–209.
27. Volovics A, Van den Brandt PA. Methods for the analyses of case-cohort studies. *Biomed J.* 1997;39:195–214.
28. Self SG, Prentice RL. Asymptotic distribution theory and efficiency results for case-cohort studies. *Ann Stat.* 1988;16:64–81.
29. Stata Corporation. Stata statistical software. Release 5.0. College Station, TX: Stata Corporation, 1997.
30. Lumey LH, Stein AD. Offspring birth weights after maternal intrauterine undernutrition: a comparison within sibships. *Am J Epidemiol.* 1997;146:810–819.
31. Noord van PA, Kaaks R. The effect of wartime conditions and the 1944-45 "Dutch famine" on recalled menarcheal age in participants of the DOM breast cancer screening project. *Ann Hum Biol.* 1991;18:57–70.
32. Dirx MJM, van den Brandt PA, Goldbohm RA, Lumey LH. Diet in adolescence and the risk of breast cancer: results of the Netherlands Cohort Study. *Cancer Causes Control.* 1999;10:189–199.
33. Jain M, Cook GM, Davis FG, Grace MG, Howe GR, Miller AB. A case-control study of diet and colorectal cancer. *Int J Cancer.* 1980;26:757–768.
34. Bristol JB, Emmett PM, Heaton KW, Williamson RCN. Sugar, fat, and the risk of colorectal cancer. *Br Med J.* 1985;291:1467–1470.
35. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control.* 1992;3:457–473.
36. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowas women (United States). *Cancer Causes Control.* 1994;8:649–667.
37. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med.* 1990;323:1664–1672.
38. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res.* 1994;54:2390–2397.

39. Gaard M, Tretli S, Loken EB. Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. *Eur J Cancer Prev.* 1996;5:445–454.
40. Goldbohm RA, Van den Brandt PA, Van 't Veer P, et al. A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res.* 1994;54: 718–723.
41. Russo A, Franceschi S, La Vecchia C, et al. Body size and colorectal-cancer risk. *Int J Cancer.* 1998;78:161–165.
42. Lee IM, Paffenbarger RS Jr. Quetelet's index and risk of colon cancer in college alumni. *J Natl Cancer Inst.* 1992;84: 1326–1331.
43. Le Marchand L, Wilkens LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. *Cancer Causes Control.* 1992;3:349–354.
44. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst.* 1997;89:948–955.
45. Nomura A, Heilbrun LK, Stemmermann GN. Body mass index as a predictor of cancer in men. *J Natl Cancer Inst.* 1985;74:319–323.
46. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med.* 1995;122:327–334.
47. Albanes D. Height, early energy intake and cancer. *Br Med J.* 1998;317:1331–1332.
48. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer — beyond physical activity. *Cancer Res.* 1997;57:75–80.
49. McKeown-Eyssen G. Epidemiology of colerectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarker Prev.* 1994;3: 687–695.
50. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control.* 1995;6:164–179.
51. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. *Cancer Epidemiol Biomarker Prev.* 2000;9:1271–1279.
52. Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid-induced inhibition of glucose uptake. *J Clin Invest.* 1994;93:2438–2446.
53. Bruce WR, Wolever TMS, Giacca A. Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. *Nutr Cancer.* 2000;37:19–26.
54. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst.* 2000;92:1472–1489.