The 1944-1945 Dutch Famine and Subsequent Overall Cancer Incidence

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Abstract

Caloric restriction seems to be the most potent dietary intervention to protect against a variety of cancers in animals. We investigated whether overall cancer risk is affected in humans after exposure to a brief famine, followed by a period of abundance. We used data of ~15,000 women who were exposed at various degrees to the 1944-1945 Dutch famine at ages between 2 and 33 years. Between 1983 and 1986, these women were asked about their individual experiences of famine exposure (''absent,'' ''moderate,'' or ''severe exposure''). During follow-up until January 2000, 1,602 new cancer cases were identified by the regional cancer registry. We assessed the relation between famine and total cancer risk by weighted Cox regression models, in which a 15% random sample was used to represent person-years lived in the entire cohort. In these models, we adjusted for potential confounders. Overall cancer risk was increased in women having been severely famine exposed compared with women having been unexposed (hazard ratio, 1.25; 95% confidence interval, 1.01-1.55). Exclusion of breast cancer cases from our analyses showed that this increase in risk was largely driven by the previously reported increase in breast cancer risk: women who were severely exposed to the famine were at a 1.12 (95% confidence interval, 0.87-1.43) times increased risk of non-breast cancer compared with the unexposed. In conclusion, we found no indications that this brief famine has affected overall cancer risk, exclusive of breast cancer. Counteracting increased caloric intake following the famine, however, may have obscured any relation. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1981–5)

Introduction

To date, caloric restriction is the most potent known dietary intervention that consistently seems to have prevented cancers in animal experiments. This knowledge dates back as far as the early 20th century (1), and involves a variety of tumors and species (2). Exactly how these effects are established remains unclear, but several mechanisms have been proposed. Oxidative stress may be reduced during caloric restriction, resulting in less reactive oxygen species that can damage DNA (3, 4). Such reactive oxygen species play an important role in tumor initiation and promotion. Furthermore, DNA repair is enhanced during caloric restriction (5) whereas cell proliferation is reduced, making cells less susceptible to DNA damage that can eventually lead to cancer (3). It has also been suggested that caloric restriction may affect cancer risk due to neuroendocrine changes, leading to hormone profiles beneficial to the host (3, 6, 7). These mechanisms involve general pathways in carcinogenesis, and if the effects of caloric restriction are also pertinent to humans, one would anticipate overall cancer risk to be reduced.

Until now, evidence that caloric restriction protects against human cancer is scarce and inconsistent. Several studies have used the adverse circumstances during World War II to explore this issue. In Norway, it seemed that the decrease in caloric intake during the war, due to rationing, resulted in decreased breast cancer risk in women who were born or were peripubertal at that time (8-11). However, we showed that a fierce famine in The Netherlands during the last year of World War II has resulted in increased risk of breast cancer, particularly if exposure was during childhood (12). Another study investigating cancer risk after this famine showed similar results for breast cancer (13), but no clear associations were found for prostate or colon cancer risk (14, 15). This famine mainly struck the densely populated western areas of The Netherlands, where daily rations per capita dropped from about 1,500 kcal in September 1944 to below 700 kcal in January (16). The famine abruptly ended with liberation on May 5th 1945, and food quickly became abundant again.

In the present study, we investigated in a large cohort of Dutch women whether this famine has subsequently affected overall cancer risk, exclusive of breast cancer. Women were classified to the degree of famine exposure based on their individual experiences. We had special interest in the timing of exposure and were able to investigate the effect of caloric restriction during different female developmental stages as these women were of ages between 2 and 33 years during the famine.

Methods

Population. In 1974, a population-based project, called Diagnostisch Onderzoek Mammacarcinoom, was started in Utrecht, The Netherlands, and its surrounding municipalities, to study the early detection of breast cancer by mammographic screening (17). This project recruited a total of 55,519 women who enrolled until 1986. Between 1983 and 1986, questionnaires were sent to 19,732 women including questions about individual experiences during the 1944-1945 Dutch famine. These women were of ages 2 to 33 years during the famine and 41 to 73 years old at interview. Women were asked about their place of residence and experiences of hunger, cold, and weight loss (''absent,'' ''moderate,'' or ''severe'') during the 1944-1945 winter. We combined these three aspects of famine into a new variable, famine score. Women who reported no exposure to at least two of these famine characteristics (''hunger,'' ''cold,'' and ''weight loss'') were categorized as ''unexposed.'' Similarly, women who reported severe exposure to at least two of these famine characteristics were categorized as ''severely

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exposed,'' and all others were categorized as ''moderately exposed'' (18). A total of 17,377 women resided in the occupied parts of The Netherlands during the famine, and for 15,396 women (89%) the famine score could be computed.

Linkage of the total cohort of 15,396 women with the registry of the Diagnostisch Onderzoek Mammacarcinoom project (from 1974) and the regional cancer registry (from 1989) provided us with all new first malignancies that occurred in the total cohort until January 2000. Basal cell and squamous cell carcinomas of the skin, as well as carcinomas *in situ*, were not included in the present analyses.

We randomly selected a sample of ~15% (n = 2,352) of the total cohort for which we ascertained vital status. These women were followed for mortality and movement out of the catchments area of the cancer registry by linkage with municipality registries until January 2000. As these women were randomly selected, their accrued person-years were used to represent the total person-years lived by the entire cohort (case-cohort design; ref. 19).

Data on reproductive events, demography, and lifestyle habits were available from questionnaires and anthropometric measures were taken by trained assistants.

Analysis. Baseline characteristics of the random sample of women are presented according to famine exposure status. For continuous variables, means with SDs or medians with ranges are presented depending on their distribution. For categorical variables we present percentages. As age at examination differed between the famine exposure categories, we explored whether any differences in baseline characteristics could be explained by this difference in age. For this we used analysis of covariance or logistic regression.

To assess the relation between famine exposure and subsequent cancer risk, we used weighted Cox regression analyses. The methods for these analyses are largely similar to a standard Cox regression and have been described by Barlow et al. (19). Follow-up time started from the famine questionnaire onwards (between 1983 and 1986) and ended at the date of diagnosis of a first malignancy (event). Women who remained free of cancer during the observation period were either censored at date of movement, date of death, or on January 1, 2000, whichever occurred first.

Analyses were done with SAS version 8.2 by use of a weighted Cox regression macro (available at http://lib.stat.cmu.edu/general/robphreg) that computes the weighted hazard ratios together with robust SEs, which we used to calculate the 95% confidence intervals (95% CI). The proportionality of the hazards assumption was evaluated with log minus log plots in SPSS 11 and found to be met. Trend tests were used to explore dose-response relations, introducing the famine score as a continuous variable (1 for unexposed, 2 for moderately exposed, and 3 for severely exposed).

We considered the following variables to be potential confounders: age at examination, body mass index (BMI) at examination (weight in kilograms divided by length in meters squared), height at examination, socioeconomic status (based on health insurance: public health, ''low''; civil servants, ''intermediate''; private, ''high''), and cigarette smoking habits (never, past, or current). Continuous variables were introduced as such in the different models and dummies were created for categorical variables. We adjusted for age at examination and age at examination squared because this described the relation of age with cancer risk best. As adjustment for cigarette smoking could be important and the measurement of smoking habits was probably not precise enough to ban residual confounding, analyses were repeated in the nonsmoking group.

The overall cancer risk after exposure to the 1944-1945 Dutch famine was first assessed, then the total risk of cancer was assessed, excluding breast cancer cases (who were censored in the analyses at the time of breast cancer diagnosis). To explore whether there are sensitive age-windows, we analyzed the relation between famine and total cancer risk, exclusive of breast cancer, separately for women exposed in early and middle childhood (2-9 years of age), later childhood and adolescence (10-18 years of age), and adulthood (over 18 years of age). These age periods are based on distinct female developmental stages as described by Bogin (20), and were specifically chosen a priori for these analyses as they allowed for reasonably sufficient numbers of cancer cases in each age category as well as for meaningful insight into sensitive developmental windows for cancer etiology. To test whether any famine effect depended on age at exposure, interaction terms were introduced into the models.

Results

At the end of the follow-up period in January 2000, 77% of the random sample of 2,352 women were still alive, 11% had died, 7% had emigrated from the region, and 5% were lost to follow-up. We had to exclude eight prevalent cancer cases from this sample as well as six women who were lost to follow-up immediately from interview onwards.

A total of 31,943 person-years were accrued in the random sample with a median follow-up of 184 months. Taking the sampling fraction into account, 212,953 person-years were estimated to have been accrued in the total cohort, during which 1,602 women were diagnosed with a first malignancy (overall cancer incidence: 7.52 per 1,000 person-years). The predominant type of cancer in this cohort was breast cancer (n = 568), followed by colon (n = 130), uterus (n = 111), and lung cancer (n = 93; Table 1).

Baseline characteristics of the random sample according to the famine score are presented in Table 2. In total, 39% of the women reported have been moderately exposed to the famine and 10% have been severely exposed. Severely famine exposed women tended to be older at the time of the famine and at examination, had a somewhat higher BMI, had generally a lower socioeconomic status, and were more often current cigarette smokers. The difference in BMI disappeared after adjustment for age at examination by analysis of covariance [adjusted means: 25.9 (unexposed), 25.8 (moderately exposed), and 25.8 (severely exposed)]. Adjustment for age attenuated the relation of famine exposure with socioeconomic status, pronounced the relation with cigarette smoking habits, and had no effect on differences in height.

Table 3 shows the relation between famine and subsequent cancer risk. Adjustment for confounding, essentially due to differences in age, seemed to be important and, hence, we only mention the fully adjusted results here. Compared with

Table 1. Site distribution of all newly diagnosed first cancers that occurred in the cohort during a median follow-up of 15 years

Cancer site	Cases, n (%)
Breast	568 (35.5)
Colon	130 (8.1)
Uterus	111 (6.9)
Lung	93 (5.8)
Ovary	87 (5.4)
Rectum	70 (4.4)
Kidney	51 (3.2)
Stomach	45 (2.8)
Pancreas	43 (2.7)
Skin (malignant melanoma)	40 (2.5)
Cervix	10 (0.6)
All other sites	354 (22.1)
Total	1,602 (100.0)

Table 2. Baseline characteristics of a random sample of the Diagnostisch Onderzoek Mammacarcinoom project according to the famine score

Characteristic	Famine score		
	Unexposed (n = 1,179)	Moderately exposed (n = 917)	Severely exposed (n = 242)
Accrued person-years of follow-up	16,293	12,476	3,174
Age at exposure (y)	15 (2-33)*	18 (2-33)	20 (4-33)
Age at examination (y)	54 (41-73)	58 (42-73)	60 (43-73)
BMI†	25.7 ± 3.9‡	25.8 ± 3.8	26.1 ± 4.3
Height† (m)	1.64 ± 0.06	1.64 ± 0.06	1.63 ± 0.07
Socioeconomic status			
Low	59.5%§	61.5%	64.0%
Intermediate	13.3%	12.6%	13.6%
High	27.1%	25.8%	22.3%
Cigarette smoking habits†			
Never smoked	67.3%§	66.3%	63.2%
Past smoker	7.1%	5.9%	4.5%
Current smoker	25.5%	27.9%	32.2%

*Median (range).
†Records with missing values—BMI: 5; height: 5; cigarette smoking habits: 1.
‡Mean ± SD.
§Percentages may not total 100% due to rounding.

women who were unexposed, the overall risk of cancer was 1.25 (95% CI, 1.01-1.55) times increased in women having been severely exposed and 1.10 (95% CI, 0.96-1.27) times increased in women having been moderately exposed (P for trend, 0.030). When we excluded breast cancer cases from the present analyses, no association between famine and cancer risk remained: non-breast cancer hazard ratio 1.12 (95% CI, 0.87-1.43) for the severely exposed and 1.07 (95% CI, 0.91-1.26) for the moderately exposed (P for trend, 0.318). To ban any residual confounding by smoking, we restricted this last analysis to women who never smoked (66% of the study population) which yielded similar, albeit attenuated, results: non-breast cancer hazard ratio 1.02 (95% CI, 0.74-1.41) for the severely exposed and 0.97 (95% CI, 0.79-1.20) for the moderately exposed (P for trend, 0.994).

We found no strong evidence that the famine had affected non-breast cancer risk in particular age groups during the famine (Table 4). However, statistical power was limited by the number of cancer cases (tests for interaction between famine exposure and age during the famine were not statistically significant).

Discussion

We showed in a cohort of close to 15,000 women with ~200,000 person-years of follow-up and 1,602 cancer cases that the circumstances during the 1944-1945 Dutch famine did not subsequently affect overall cancer risk, exclusive of breast cancer.

To appreciate these findings, we would like to address some strengths and limitations of our study. Although a black page in Dutch history, the 1944-1945 Dutch famine presently enables us to study the long-term effects of a short but fierce famine on human health in an otherwise well-nourished population, and address possible differential effects by ages at exposure. We could classify women according to famine exposure on an individual basis, which gives a better classification compared with the use of residential area as a proxy. Nevertheless, because the individual score is based on recall, misclassification may have occurred. Most likely, this would be unrelated to cancer risk as women filled out the famine questionnaires before a possible cancer diagnosis and thus unaware of whether they would develop cancer during the follow-up period or not. Such misclassification would therefore be random and eventually result in an underestimation of the true famine effects. The famine score shows a good correlation with degree of urbanization during the famine (18): women who resided in rural areas were less frequently severely exposed compared with women who resided in urban areas. Furthermore, women who were severely exposed tended to be older during the famine (Table 2). Both associations are in line with the historical situation where the famine was worst in the large cities and the young were relatively protected by their families, official

Table 3. Famine and subsequent cancer risk

Famine score	Cancer cases, n	Person-years*	Crude model	Adjusted model†
			Hazard ratio (95% CI)	Hazard ratio (95% CI)
All cancer sites‡				
Unexposed	718	108,580	1.00	1.00
Moderately exposed	669	82,780	1.22 (1.07-1.40)	1.10 (0.96-1.27)
Severely exposed	212	21,160	1.53 (1.25-1.88)	1.25 (1.01-1.55)
P for trend			<0.001	0.030
All cancer sites, exclusive of breast cancer§				
Unexposed	459	108,580	1.00	1.00
Moderately exposed	439	82,780	1.25 (1.07-1.47)	1.07 (0.91-1.26)
Severely exposed	134	21,160	1.51 (1.20-1.91)	1.12 (0.87-1.43)
P for trend			<0.001	0.318

*Adjusted for age at examination, age at examination squared, BMI, height, socioeconomic status, and cigarette smoking habits.
†Lived in the total cohort (extrapolated from the random sample).
‡Five random sample participants and three cancer cases were excluded from these analyses because of missing data on covariables.
§Five random sample participants and two cancer cases were excluded from these analyses because of missing data on covariables.

Table 4. Famine and subsequent cancer risk, exclusive of breast cancer, according to age during famine

Famine score	Cancer cases, *n*	Person-years*	Crude model	Adjusted model†
			Hazard ratio (95% CI)	Hazard ratio (95% CI)
Aged 2-9 y during famine				
Unexposed	78	32,736	1.00	1.00
Moderately exposed	45	17,075	1.10 (0.73-1.65)	1.09 (0.71-1.66)
Severely exposed	12	2,461	2.08 (1.01-4.27)	1.48 (0.68-3.23)
P for trend			0.125	0.364
Aged 10-18 y during famine				
Unexposed	145	41,805	1.00	1.00
Moderately exposed	103	27,625	1.08 (0.81-1.44)	1.07 (0.80-1.45)
Severely exposed	27	6,683	1.18 (0.73-1.91)	1.12 (0.68-1.85)
P for trend			0.444	0.571
Aged over 18 y during famine				
Unexposed	236	34,039	1.00	1.00
Moderately exposed	291	38,080	1.10 (0.88-1.36)	1.05 (0.84-1.31)
Severely exposed	95	12,015	1.14 (0.84-1.54)	1.03 (0.75-1.40)
P for trend			0.327	0.781

NOTE: Five random sample participants and three cancer cases were excluded from these analyses because of missing data on covariables.
*Lived in the total cohort (extrapolated from the random sample).
†Adjusted for age at examination, age at examination squared, BMI, height, socioeconomic status, and cigarette smoking habits.

rations, and charity organizations (16, 21). From these circumstantial data, we conclude that the famine score is reasonably accurate in measuring true famine exposure status.

Adjustment of confounding may have been inadequate because the analysis combines various types of malignancies with different risk profiles. For instance, smoking is strongly associated with lung cancer (22), but not (as strong) with other types of cancer. The actual relation between smoking and lung cancer is therefore underestimated by the model and this could have lead to residual confounding, whereas the actual relation between smoking and other types of cancer may be overestimated, which could have led to overadjustment. To tackle this problem for smoking, we reanalyzed the data in women who never smoked. This did not change our results.

It could be that confounding by other lifestyle factors that we did not take into account may also be of importance. However, many of such lifestyle factors (e.g., alcohol use) cluster with socioeconomic status and cigarette smoking, for which we did adjust in the analyses. Furthermore, the most important confounder in our data was the age at examination, besides which lifestyle factors such as cigarette smoking habits and BMI did not contribute substantially to risk estimate changes. It is therefore unlikely that confounding by other lifestyle factors unaccounted for has caused a substantial bias in our study.

There are no previous reports on wartime conditions and total cancer risk, and results have been contradictory for subtypes (8-15). Anorexia patients have also been studied to relate caloric restriction to human cancer risk. Overall cancer risk seemed to be lower than expected (23), as well as breast cancer risk (23, 24), but these studies involved very few cancer cases, limiting strong conclusions. Furthermore, generalization of these results is hampered by the highly selective nature of this patient group.

Besides the above-mentioned situations of severe nutritional deprivation, there is some data on the effect of calorie intake within ''normal'' ranges on cancer risk. A British study in the Boyd Orr cohort showed that the overall cancer mortality risk increased with daily calorie intake during childhood (hazard ratio, 1.15; 95% CI, 1.06-1.24 per megajoule increase in intake; ref. 25). In addition, a high BMI during adulthood, the result of high energy intake relative to low energy expenditure, relates to higher cancer mortality (26).

Our study lacked the power to investigate the relation between the famine and risk of specific types of cancer, other than that of the breast on which we reported elsewhere (12). Even so, an effect on overall cancer risk could be anticipated, given the fact that most of the proposed mechanisms by which caloric restriction may protect against cancer are mechanisms generally involved in carcinogenesis. However, the Dutch famine was quickly followed by a period of sufficient food and it seems that those who were severely exposed to the famine have made up for the lost calories as their average BMI at examination between 1983 and 1986 was similar to that of the unexposed. We may therefore be looking not solely at caloric restriction but at the combined effects of caloric restriction and possibly counteracting increased food intake, a combination that could have led to the increase of breast cancer risk in women who were 2 to 9 years old during the famine (12). Besides that, it may very well be that the duration of the famine (i.e., 6 months) was too short for caloric restriction to exert any effect on overall cancer risk, exclusive of breast cancer. Prolonged or lifetime exposure to caloric restriction may be more important with regard to cancer risk. That we found no evidence for any sensitive time windows for the effect of famine within the age range of 2 to 33 years used in our study does not preclude any effect of famine during other critical periods such as fetal life. It actually also does not preclude that there are sensitive time windows within the age range that we studied, but here, again, the Dutch famine may have lasted too shortly for these sensitive periods to become visible.

In conclusion, our findings do not support the view that the 1944-1945 Dutch famine has subsequently resulted in decreased overall cancer risk. Because we previously have shown breast cancer risk to be increased after the famine (12), this could indicate that any effect of the famine on cancer risk does not operate through mechanisms that are generally involved in human carcinogenesis. Further research is needed to investigate the effects of famine on specific types of cancer to further elucidate this issue.

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