Breast Cancer Risk After Caloric Restriction During the 1944–1945 Dutch Famine

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Background: **Data from animal models suggest that caloric restriction may reduce the risk of breast cancer, although not all dietary regimens produce similar effects. We examined whether caloric restriction imposed as a consequence of the 1944–1945 Dutch famine reduced the risk of breast cancer in women participating in a Dutch breast cancer screening program.** ***Methods:*** **Between 1983 and 1986, approximately 15 000 women, aged 2 to 33 years during the 1944–1945 Dutch famine, responded to a questionnaire about their famine experience. A famine exposure score, graded as absent, moderate, or severe exposure, was derived from answers regarding hunger, cold, and weight loss. During follow-up until January 2000, 585 women with incident breast cancer were identified by the regional cancer registry. The relationship between famine exposure and breast cancer risk was assessed by weighted Cox regression models, in which person-years lived for the entire cohort was extrapolated from data from a random sample of 15% of the cohort.** ***Results:*** **Women who were severely exposed to the famine had a statistically significantly higher risk of breast cancer (hazard ratio [HR] = 1.48, 95% confidence interval [CI] = 1.09 to 2.01) than women who were not exposed. Women who were moderately exposed to the famine had a 13% increased risk of breast cancer (HR = 1.13, 95% CI = 0.92 to 1.38; P_{trend} = 0.016). The association between famine exposure and breast cancer risk was stronger for women who were exposed between the ages of 2 and 9 years (severely exposed versus unexposed: HR = 2.01, 95% CI = 0.92 to 4.41) than for women who were exposed at older ages.** ***Conclusions:*** **The risk of breast cancer was increased in women who were severely exposed to a short but severe famine decades earlier. This result is compatible with data from the few animal studies investigating effects of short-term, transient caloric restriction. [J Natl Cancer Inst 2004; 96:539–46]**

It has been known for some time that caloric restriction can be a potent and highly reproducible way to prevent various types of cancer, including breast cancer, in rodents. Indeed, one of the first reports of such an observation was published in 1909 *(1)*, and other studies *(2–4)* subsequently followed. The relationship between caloric restriction and cancer prevention is not fully understood but may involve several mechanisms, including increased DNA repair activity, reduced cell proliferation resulting from decreased availability of energy, and reduced oxidative stress *(5)*. Hormonal changes may also be involved *(5)* through effects of caloric restriction on the hypothalamic–pituitary axis *(6,7)*.

In the majority of animal models evaluating energy restriction and cancer risk, animals are subjected to lifelong dietary interventions *(2)*. Animal data on short-term, transient caloric restriction and cancer risk are scarce and inconclusive *(8–13)*. Few human studies on the relationship between substantial energy restriction and breast cancer risk have been performed, in part, because such a relationship is ethically difficult to investigate. However, in extreme situations such as war, opportunities arise to address the impact of short-term, transient energy restriction. Indeed, several studies have linked breast cancer risk to the experiences of women during World War II. For example, the average daily caloric intake in Norway declined from 3475 kilocalories in 1939 to a minimum of 2700 kilocalories in 1944–1945 *(14,15)*. Results from four Norwegian studies *(16–19)* suggest that a decreased risk of breast cancer is associated with such a decreased caloric intake.

Many people residing in the densely populated western parts of The Netherlands experienced a severe famine at the end of World War II. The famine was the result of an accumulation of several circumstances. By September 1944, the Allied forces had liberated the southern part of The Netherlands and tried to end the war quickly with an offensive aimed at capturing the Rhine bridge at Arnhem; a capture would facilitate an advance into the Ruhr area *(20)*. To thwart the transport of German troops and ammunition, the exiled Dutch government ordered a railroad strike. German authorities responded to the strike with a food embargo that specifically affected the western parts of The Netherlands. The Allied offensive failed, and the abundance and availability of food deteriorated rapidly. Official daily adult *per capita* rations, which were roughly sufficient during the first 4 years of the war, decreased from approximately 1500 kilocalories in September 1944 to less than 700 kilocalories in January 1945. During this period, the relative amounts of protein, fat, and carbohydrate remained more or less balanced. Many residents of the large western Dutch cities undertook long and exhaustive journeys to the countryside in search of food. The famine situation began to improve on April 29, 1945, when food was airlifted and dropped over the region. Food again became abundant with the liberation of The Netherlands on May 5, 1945 *(21,22)*.

In contrast to the Norwegian studies *(16–19)*, a Dutch study investigating the relation between the famine of 1944–1945 and subsequent breast cancer risk *(23)* found no decreased risk. However, that study used "place of residence" during the famine as a proxy for individual famine exposure. In this analysis, we have used individual exposure data from women participating in

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See "Notes" following "References."

DOI: 10.1093/jnci/djh087

Journal of the National Cancer Institute, Vol. 96, No. 7,

a large, population-based breast cancer–screening cohort to investigate the effect of the 1944–1945 Dutch famine on subsequent breast-cancer risk. We were able to examine this relation during different stages of female development, because the women in this cohort were aged 2–33 years during the Dutch famine that lasted for a relatively short period of time (i.e., 6 months).

Subjects and Methods

Population

In 1974, a population-based prospective cohort study *(24)* for the early detection of breast cancer, the Diagnostisch Onderzoek Mammacarcinoom (DOM) project, started in Utrecht and surrounding municipalities in The Netherlands. Between 1974 and 1986, the DOM project recruited a total of 55 519 women who were born between 1911 and 1945. Participation in the project was voluntary. Depending on their year of birth, the women were offered mammographic screening at different intervals and at different ages, and formed four distinct cohorts: DOM-1, women born between 1911 and 1925 and recruited between 1974 and 1979; DOM-2, women born between 1926 and 1931 and recruited between 1981 and 1982; DOM-3, women born between 1932 and 1941 and recruited between 1982 and 1985; and DOM-4, women born between 1942 and 1945 and recruited between 1985 and 1986. The overall participation rate was 70% (range = 44%–72%). During the screening examinations that took place between 1983 and 1986, the 19 732 women who were still participating in the DOM project were sent questionnaires seeking information on their personal experiences during the 1944–1945 Dutch famine. These women were aged 41–73 years at the time they responded to the questionnaires and were born between 1911 and 1941. Women in the DOM-4 cohort did not receive this questionnaire because they were too young during the famine to remember their own experiences. Participants were asked about their place of residence during the famine and about their personal experience with hunger, cold, and weight loss during the famine. The participants were asked to grade their famine experiences as "absent," "moderate," or "severe." We combined the answers to the three personal experience questions into a new variable, which we called the famine score. Women who answered "severe" to at least two of the three questions were categorized as "severely exposed." Similarly, women who answered "absent" to at least two of the three questions were categorized as "unexposed." All other women were categorized as "moderately exposed" *(25)*.

Of the 19 732 women who received the questionnaire, we excluded 2355 women who resided in the liberated region in the southern part of The Netherlands or abroad at the time of the famine. We thus included all women who resided in the occupied parts of The Netherlands during the winter of 1944–1945. A famine score could be computed for 15 396 women (89%).

By linking the total cohort of 15 396 women with the DOM project cancer registry (established in 1974) and the regional cancer registry (established in 1989), we identified all primary invasive breast cancers, excluding carcinoma *in situ*, that occurred in the cohort until January 1, 2000. Because assessing vital status at follow-up is costly and time-consuming, we chose the efficiency of a case–cohort study design, in which a random sample of the total cohort is used to represent total person-years lived for the entire cohort *(26)*. As in a prospective cohort analysis, all breast cancer cases occurring in the entire cohort contribute to the dataset, but only a sample of the total cohort is needed to estimate the number of person-years lived. We randomly selected a sample of approximately 15% of the total cohort (n = 2352) for which we ascertained vital status. This random sample of women was followed until January 1, 2000, by using regional municipality registries for mortality and movement out of the catchment area of the cancer registry.

Data on reproductive events, demographics, and breast cancer risk factors were available from questionnaires obtained during the screening examinations, at which time trained medical assistants also took anthropometric measures. Women gave oral informed consent, and the study was approved by the institute's ethical committee.

Statistical Analysis

Characteristics of the random sample of women at baseline (i.e., at the time the completed famine questionnaire was received) are presented according to famine exposure status. For continuous variables, means with standard deviations are presented. Continuous variables were also dichotomized on the basis of their median values within the total random sample, except for age at screening examination, which was categorized by quartiles. For categorical variables, we present the total number of random-sample participants in each category, the total number of cases that occurred in the entire cohort, and the estimated number of person-years lived for the entire cohort. The case–cohort design allows assessment of absolute incidence rates, which we adjusted for age. For this adjustment, we used the direct standardization method, in which the age distribution of the random sample of women served as the standard.

To assess the relation between famine and breast cancer risk, we used weighted Cox proportional hazards regression analyses. The methods for these analyses are similar to the standard Cox proportional hazards regression analyses and have previously been described by Barlow et al. *(26)*. Follow-up time started with the date the completed famine questionnaire (administered between 1983 and 1986) was received and ended with the date of a primary invasive breast cancer diagnosis (event). Women who remained free of breast cancer during the observation period were censored at the date of emigration from the catchment area, the date of death from any cause, or the end of follow-up (January 1, 2000), whichever occurred first.

Analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC) by use of a weighted Cox regression macro [*(26)*, available at http://lib.stat.cmu.edu/general/robphreg] that computes the weighted estimates together with a robust standard error. From these standard errors, we calculated 95% confidence intervals (CIs). The proportionality of the hazards over time was evaluated with log minus log plots in SPSS 11 (SPSS, Chicago, IL), and assumptions of proportionality were 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 as potential confounders: age at menarche, age at screening examination (i.e., when the completed famine questionnaire was received), body mass index at screening examination (weight in kilograms divided by height in meters squared), height at screening examination,

parity (nulliparous or parous), age at first childbirth, socioeconomic status (derived from health insurance information, for which women who used the public service were considered to be of low socioeconomic status, civil servants were considered to be of intermediate socioeconomic status, and those who had private insurance were considered to be of high socioeconomic status), and family (first-degree relative [mother or sister]) history of breast cancer (yes or no). Age at menopause was also considered to be a confounder, but we could assess its potential confounding effects only for a subgroup of women for whom the information on age at menopause was available. Continuous variables were introduced as such in the different models, and categorical variables were introduced as dummy variables. We adjusted for age at screening examination and its square, because these two variables were found in preliminary analyses to best describe the relation between age and breast cancer risk. To include age at first childbirth and parity simultaneously in the models, we used the age at first childbirth centered around its mean multiplied by parity *(27,28)*.

To assess whether differences in breast cancer risk were associated with developmental stage, we analyzed the relationship between famine exposure and breast cancer risk separately for women exposed in early and middle childhood (aged 2–9 years), later childhood and adolescence (aged 10–18 years), and adulthood (aged ≥19 years). These age groups are based on distinct female developmental stages as described by Bogin *(29)*. Age during the famine was determined relative to the date the famine started (October 1, 1944) and resulted in an age range during the famine that varied between 2 and 33 years.

Because pregnancy is known to alter the neuroendocrine milieu *(30)* and we have previously found that exposure to the famine was associated with increased levels of sex steroids in postmenopausal nulliparous women but not in parous women *(31)*, we evaluated whether a relation between the famine exposure and breast cancer risk was modified by parity. Interaction terms were introduced into the models to test any observed associations.

RESULTS

At the end of the follow-up (January 1, 2000), 77% of the random sample of 2352 women were still alive, 11% had died, 7% had emigrated from the catchment area, and 5% were lost to follow-up. We excluded 11 women from the random sample because six women were lost to follow-up immediately following their screening examination and five women had a history of breast cancer.

A total of 32 357 person-years were accrued in the random sample, with a median time of follow-up of 184 months (15.3 years). By extrapolation, 215 714 person-years were accrued in the total cohort, during which 585 women were diagnosed with primary invasive breast cancer. By using this number of diagnoses, we calculated an overall breast cancer incidence rate of 2.71 per 1000 person-years. According to data from the Netherlands Cancer Registry *(32)*, the breast cancer incidence rate in 1997 among similar aged women from the general Dutch population was 2.75 per 1000 person-years. Thus, follow-up of the breast cancer cases in our cohort was largely complete.

The median age at diagnosis among all women with breast cancer was 64 years. A total of 487 women were postmenopausal when diagnosed with breast cancer, whereas seven women were premenopausal when diagnosed with breast cancer. The menopausal status of an additional 91 women diagnosed with breast cancer was unknown. The median age at diagnosis of the 91 women with unknown menopausal status was 52 years. Thus, the majority of the breast cancer cases in our study were diagnosed in postmenopausal women.

Baseline characteristics of the random sample of women according to famine exposure are presented in Table 1. Among this sample of women, 10% reported severe exposure and 39% reported moderate exposure to the famine. The women who reported severe exposure were, on average, older during the famine and at the screening examination, had a higher body mass index, reached menopause at a younger age, gave birth to their first child at an earlier age, and had a lower socioeconomic status than the women in the other exposure groups.

The risk of breast cancer increased with increasing famine exposure. Age-adjusted breast cancer incidence rates were 2.48 per 1000 person-years for women who were not exposed to the famine, 2.80 per 1000 person-years for women who were moderately exposed, and 4.05 per 1000 person-years for women who were severely exposed. After adjusting for additional variables, women who were moderately exposed to the famine had a 13% (hazard ratio [HR] = 1.13, 95% CI = 0.92 to 1.38) higher risk of breast cancer, and women who were severely exposed had a 48% (HR = 1.48, 95% CI = 1.09 to 2.01) higher risk of breast cancer than women who were not exposed (P_{trend} = .016; Table 2).

In an additional analysis, we adjusted for age at menopause in a sample of women for which this information was available (488 women with breast cancer and 2051 random-sample participants). The hazard ratios were similar to those in the analysis without this adjustment and suggest that age at menopause did not appear to confound the results (data not shown).

We next determined whether there was an association between age during the famine, breast cancer risk, and famine exposure (Table 3). The association between famine exposure and breast cancer risk, although not statistically significant, was in the same direction for all age groups. The largest impact of famine exposure on breast cancer risk was seen for women who were exposed at a young age. Compared with the risk of breast cancer in women who were not exposed to the famine, the risk in women who were severely exposed to the famine between the ages of 2 to 9 years was doubled (HR = 2.01, 95% CI = 0.92 to 4.41). The risk of breast cancer was also increased in women who were severely exposed to the famine at later ages (HR = 1.55, 95% CI = 0.89 to 2.73 for women aged 10–18 years during the famine, and HR = 1.18, 95% CI = 0.77 to 1.80 for women aged ≥19 years during the famine). Among women who were aged 2–9 years during the famine, the association between severe exposure and breast cancer risk was not statistically significantly different from that among women aged 19 years or older during the famine (test for interaction: P = .06).

The relationship between famine exposure and breast cancer risk was stronger for nulliparous women than for parous women (Table 4). Among nulliparous women, those who were severely exposed to the famine had a more than twofold increased risk (HR = 2.02, 95% CI = 0.92 to 4.42) of breast cancer compared with those who were not exposed to the famine. Among parous women, those who were severely exposed to famine had a 38% (HR = 1.38, 95% CI = 0.99 to 1.93) increased risk of breast cancer compared with those who were not exposed to the fam-

Table 1. Baseline characteristics of a random sample of participants from the Diagnostisch Onderzoek Mammacarcinoom (DOM) project according to the famine score*

Characteristic	Famine score: Not exposed (n = 1181) No. (%)	Not exposed (n = 1181) No. of cancers in total cohort/total No. of person-years†	Moderately exposed (n = 918) No. (%)	Moderately exposed (n = 918) No. of cancers in total cohort/total No. of person-years	Severely exposed (n = 242) No. (%)	Severely exposed (n = 242) No. of cancers in total cohort/total No. of person-years	Age-adjusted breast cancer incidence rate/1000 person-years‡
Age during famine, y							
Median (range)		15 (2–33)		18 (2–33)		20 (4–33)	
<17	673 (57)	144/64 745	385 (42)	111/36 973	83 (34)	34/7515	2.65
≥17	508 (43)	123/45 253	533 (58)	126/47 329	159 (66)	47/13 900	2.78
Age at menarche, y							
Mean (standard deviation)		13.7 (1.6)		13.6 (1.5)		13.7 (1.7)	
<13	289 (24)	66/26 927	230 (25)	73/20 952	59 (24)	28/5175	3.14
≥13	892 (76)	201/83 070	688 (75)	164/63 349	183 (76)	53/16 240	2.58
Age at screening examination, y							
Median (range)		54 (41–73)		58 (42–73)		60 (43–73)	
<51	373 (32)	90/36 351	200 (22)	63/19 771	34 (14)	15/3318	2.83
51–56	310 (26)	60/26 609	197 (21)	46/18 729	57 (24)	20/4969	2.36
57–62	276 (23)	57/25 275	256 (28)	62/23 146	56 (23)	22/5158	2.63
>62	222 (19)	60/18 763	265 (29)	66/22 655	95 (39)	24/7970	3.04
Body mass index, kg/m^2§							
Mean (standard deviation)		25.7 (3.9)		25.8 (3.8)		26.1 (4.3)	
<25	502 (43)	116/47 135	366 (40)	90/34 132	90 (37)	36/8102	2.72
≥25	678 (57)	151/62 818	548 (60)	147/49 829	152 (63)	44/13 313	2.70
Height, m§							
Mean (standard deviation)		1.64 (0.06)		1.64 (0.06)		1.63 (0.07)	
<1.64	546 (46)	121/50 710	448 (49)	99/40 775	125 (52)	33/10 960	2.43
≥1.64	634 (54)	146/59 243	466 (51)	138/43 186	117 (48)	47/10 455	3.01
Age at menopause, y§							
Mean (standard deviation)		49.2 (4.5)		49.1 (4.7)		48.1 (5.5)	
<50	457 (44)	87/41 733	368 (44)	77/34 603	108 (47)	33/9855	2.27
≥50	591 (56)	127/55 420	477 (56)	128/42 799	120 (53)	42/10 333	2.62
Parity							
Nulliparous	147 (12)	38/13 214	165 (18)	43/14 599	30 (12)	15/2851	3.14
Parous	1034 (88)	229/96 784	753 (82)	194/69 703	212 (88)	66/18 564	2.65
Age at first birth, y§,‖							
Mean (standard deviation)		26.9 (4.2)		26.9 (4.2)		26.2 (4.2)	
<26	412 (40)	79/37 734	297 (39)	77/27 577	101 (48)	26/8756	2.50
≥26	622 (60)	150/59 050	455 (61)	117/42 024	111 (52)	40/9808	2.77
Socioeconomic status							
Low	704 (60)	156/65 856	564 (61)	155/50 938	155 (64)	58/13 719	2.82
Intermediate	157 (13)	28/14 433	116 (13)	26/11 094	33 (14)	11/2853	2.39
High	320 (27)	83/29 709	238 (26)	56/22 270	54 (22)	12/4842	2.68
Family history of breast cancer§							
Mother							
No	1129 (96)	241/105 428	863 (95)	213/79 263	230 (95)	73/20 367	2.57
Yes	48 (4)	24/4200	50 (5)	22/4556	12 (5)	7/1048	5.56
Sister(s)							
No	1125 (95)	241/104 942	870 (95)	222/79 739	223 (92)	72/19 719	2.62
Yes	55 (5)	26/4973	47 (5)	14/4464	19 (8)	9/1696	4.50

*Famine scores were derived from three separate questions regarding experiences of weight loss, hunger, and cold, graded "absent," "moderate," or "severe." Women who answered "severe" to at least two of the three questions were categorized as "severely exposed." Women who answered "absent" to at least two of the three questions were categorized as "not exposed." All other women were categorized as "moderately exposed." Cutoff points for age at exposure, age at menarche, body mass index (weight in kilograms divided by height in meters squared), height, age at menopause, and age at first childbirth were the median values of the total random sample; cutoff points for age at examination were according to quartiles.

†The total number of breast cancer cases that occurred during the follow-up time within the entire cohort of 15 396 women together with the number of person-years lived (extrapolated from the 15% random sample).

‡Rates were adjusted for age by the direct standardization method, in which the age distribution of the random sample served as the standard (rates for age at exposure were not adjusted for age at screening examination because of high correlation).

§Missing values: body mass index, five participants from the random sample and one participant with breast cancer from the total cohort; height, five participants from the random sample and one participant with breast cancer from the total cohort; age at menopause, 210 participants from the random sample and 91 participants with breast cancer from the total cohort (including 10 breast cancer cases from the random sample); age at birth of first child, one participant from the random sample; mother's history of breast cancer, nine participants from the random sample and five participants with breast cancer from the total cohort; history of breast cancer, two participants from the random sample and one participant with breast cancer from the total cohort. Records with missing values for body mass index, age at birth of first child, maternal breast cancer or affected sister(s) were excluded from all further analyses (16 random sample participants and seven breast cancer cases from the total cohort).

‖Among women who were parous.

Table 2. Famine and subsequent breast cancer risk during a median follow-up of 15 years*

Famine score	No. of breast cancer cases	Person-years†	Hazard ratio (95% CI)		
			Crude model	Age-adjusted model‡	Fully adjusted model§
Not exposed	265	109 502	1.00 (referent)	1.00 (referent)	1.00 (referent)
Moderately exposed	234	83 376	1.17 (0.96 to 1.42)	1.15 (0.94 to 1.40)	1.13 (0.92 to 1.38)
Severely exposed	79	21 415	1.54 (1.16 to 2.05)	1.49 (1.11 to 2.01)	1.48 (1.09 to 2.01)
P_{trend}			.004	.009	.016

*Famine scores were derived from three separate questions regarding experiences of weight loss, hunger, and cold, graded "absent," "moderate," or "severe." Women who answered "severe" to at least two of the three questions were categorized as "severely exposed." Women who answered "absent" to at least two of the three questions were categorized as "not exposed." All other women were categorized as "moderately exposed." The 16 participants from the random sample and seven participants with breast cancer from the total cohort for whom covariable data were missing were excluded from these analyses.

†Person-years lived in the total cohort, which was extrapolated from data collected from the random sample.

‡Adjusted for age at screening examination and age at screening examination squared.

§Adjusted for age at screening examination and age at screening examination squared, body mass index, height, socioeconomic status, age at menarche, parity, age at birth of first child and family history of breast cancer (first-degree relative).

ine. However, tests for interaction were not statistically significant.

DISCUSSION

Caloric restriction over a period of 6 months, as endured during the 1944–1945 Dutch famine, was associated with an increased risk of breast cancer decades later. The association seemed to be stronger in 1) women who were younger than 10 years when exposed to the famine than in women who were older and 2) nulliparous women than in parous women.

Although the 1944–1945 famine is a black page in Dutch history, it provides a unique situation in which to study the long-term consequences of a short but severe famine in humans. We explored the relation between famine exposure and breast cancer risk in a cohort of approximately 15 000 women, with approximately 200 000 person-years of follow-up and 585 primary invasive breast cancers. We analyzed individual famine-exposure data, which may be more accurate than area-exposure data, in which all women in a specific area are assigned to the same exposure status. However, the individual exposure scores in our study were derived from subjective information and were based on individual recall, and thus may be subject to misclassification. Because the women reported their famine experiences years before any breast cancers were diagnosed, it is unlikely that recall would be related to subsequent breast cancer risk. Random misclassification would have resulted in an underestimation of the true effects; such underestimates may be greatest in those women who were the youngest during the famine because their recall of famine experiences is likely to be the least accurate.

Severe famine exposure was reported more frequently by women who lived in urban areas during the famine than by women who lived in rural areas *(25)*. This result was expected on the basis of historical information reporting that the famine was worse in large cities *(21)*. Furthermore, women who were severely exposed to the famine were, on average, older during the famine than women who were not exposed. During the entire war period and during the famine, rations were provided on the basis of age and were aimed at providing relative protection to

Table 3. Famine and subsequent breast cancer risk according to age during famine*

Age group and famine score	No. of breast cancer cases	Person-years†	Hazard ratio (95% CI)	
			Crude model	Adjusted model‡
Aged 2–9 years during famine				
Not exposed	77	32 818	1.00 (referent)	1.00 (referent)
Moderately exposed	49	16 985	1.23 (0.82 to 1.83)	1.14 (0.74 to 1.76)
Severely exposed	14	2465	2.44 (1.25 to 4.76)	2.01 (0.92 to 4.41)
P_{trend}			.023	.121
Aged 10–18 years during famine				
Not exposed	91	42 265	1.00 (referent)	1.00 (referent)
Moderately exposed	70	27 929	1.16 (0.83 to 1.64)	1.24 (0.86 to 1.78)
Severely exposed	23	6764	1.59 (0.95 to 2.68)	1.55 (0.89 to 2.73)
P_{trend}			.089	.090
Aged 19 years or older during famine				
Not exposed	97	34 419	1.00 (referent)	1.00 (referent)
Moderately exposed	115	38 461	1.08 (0.80 to 1.46)	1.04 (0.76 to 1.42)
Severely exposed	42	12 186	1.25 (0.83 to 1.88)	1.18 (0.77 to 1.80)
P_{trend}			.306	.482

*Famine scores were derived from three separate questions regarding experiences of weight loss, hunger, and cold, graded "absent," "moderate," or "severe." Women who answered "severe" to at least two of the three questions were categorized as "severely exposed." Women who answered "absent" to at least two of the three questions were categorized as "not exposed." All other women were categorized as "moderately exposed." The 16 participants from the random sample and seven participants with breast cancer from the total cohort for whom covariable data were missing were excluded from these analyses.

†Person-years lived in the total cohort, which was extrapolated from data collected from the random sample.

‡Adjusted for age at screening examination and age at screening examination squared, body mass index, height, socioeconomic status, age at menarche, parity, age at birth of first child and family history of breast cancer (first-degree relative).

Table 4. Famine and subsequent breast cancer risk according to parity*

Parity and famine score	No. of breast cancer cases	Person-years†	Hazard ratio (95% CI)	
			Crude model	Adjusted model‡
Nulliparous				
Not exposed	38	13 214	1.00 (referent)	1.00 (referent)
Moderately exposed	43	14 497	1.04 (0.64 to 1.70)	1.06 (0.63 to 1.77)
Severely exposed	15	2851	1.86 (0.91 to 3.78)	2.02 (0.92 to 4.42)
P_{trend}			.193	.174
Parous				
Not exposed	227	96 288	1.00 (referent)	1.00 (referent)
Moderately exposed	191	68 879	1.18 (0.96 to 1.46)	1.15 (0.92 to 1.43)
Severely exposed	64	18 564	1.48 (1.08 to 2.03)	1.38 (0.99 to 1.93)
P_{trend}			.010	.046

*Famine scores were derived from three separate questions regarding experiences of weight loss, hunger, and cold, graded "absent," "moderate," or "severe." Women who answered "severe" to at least two of the three questions were categorized as "severely exposed." Women who answered "absent" to at least two of the three questions were categorized as "not exposed." All other women were categorized as "moderately exposed." The 16 participants from the random sample and seven participants with breast cancer from the total cohort for whom covariable data were missing were excluded from these analyses.

†Person-years lived in the total cohort, which was extrapolated from data collected from the random sample.

‡Adjusted for age at examination and age at examination squared, body mass index, height, socioeconomic status, age at menarche, age at birth of first child, (except for analysis within nulliparous women), and family history of breast cancer (first-degree relative).

the young *(22)*. From these circumstantial data, we conclude that the individual famine score is quite accurate in measuring true famine exposure status.

A methodologic shortcoming of our study is that the results are conditional on the women surviving until the screening examinations that were conducted between 1983 and 1986, approximately 40 years after the famine. We can only speculate what effects this could have had on our findings. Although an estimated 22 000 people died of starvation during the famine, mortality data from Amsterdam, a large city that was severely struck by the famine, showed that 75% of all deaths were male and 79% of all deaths were either babies (aged ≤1 year) or the elderly (aged ≥65 years) *(21)*. A direct increase in mortality resulting from the famine in the source population for our study was therefore minimal (female cohort, aged 2–33 years during the famine). Furthermore, the overall life expectancy of women born between 1930 and 1942 (aged between 2 and 14 years during the famine) did not deviate substantially from what was expected, based on the trend of increased life expectancy during the last century *(33)*. Even if the famine did decrease survival until the screening examination, it is unlikely that this was related to the risk of developing breast cancer. Therefore, we believe that conditional survival was not related to famine experiences or to subsequent breast cancer risk and therefore could not have influenced the results.

We were not able to adjust for alcohol use in our analyses because this information was not available. A recent meta-analysis *(34)* reported that the relative risk of breast cancer increased by 7.1% for every 10 g of alcohol consumed per day. Thus, to fully explain our findings that severe famine exposure is associated with twice the risk of breast cancer in women aged 2–9 years during the famine, women who were severely exposed to the famine would, on average, have to consume approximately 100 g of alcohol or 10 drinks per day more than the amount of alcohol consumed by women who were not exposed to the famine. Women in western countries drink an average of 6.0 g of alcohol per day, and only 1.3% of women drink more than 45 g of alcohol per day *(34)*. Thus, it seems unlikely that alcohol use could have confounded our results to any great extent.

Although considerable evidence showed that prolonged caloric restriction reduced mammary tumor risk in rodents *(3,4)*, the short but severe caloric restriction imposed by the 1944–1945 Dutch famine was associated with an increased risk of breast cancer in humans. The only other report on the Dutch famine and its association with breast cancer risk by Dirx et al. *(23)* used place of residence as a proxy for famine exposure rather than individual recall of famine exposure, and it showed equivocal effects. Compared with women who lived in a non-western area during the famine, women who lived in a western rural area had a 1.5-fold (95% CI = 1.1-fold to 1.9-fold) increased risk for breast cancer, and women who lived in a western city had a 1.1-fold (95% CI = 0.9-fold to 1.4-fold) increased risk for breast cancer. Because the women in the study by Dirx et al. *(23)* were already aged 13 years or older during the famine, the authors were not able to explore the impact of famine during childhood on breast cancer risk.

Four studies *(16–19)* have indirectly associated breast cancer risk with the 1940–1945 wartime conditions in Norway, when caloric intake was substantially reduced. Two studies *(18,19)* showed that women who were peripubertal during the war had a lower than expected incidence of breast cancer. Two other studies described the relation between adult height and breast cancer risk and showed that a positive relation was more pronounced in women who were born during the war years *(17)* or who were peripubertal during this period *(16)*. These observations have led to the conclusion that dietary factors early in life that subsequently affect adult height may play a role in the etiology of breast cancer.

The association between caloric intake and subsequent breast cancer risk has been investigated in women with extremely low (anorexia nervosa) or high (obesity) body mass indices. Although the risk of breast cancer was 20% lower than expected in patients with anorexia nervosa, the observation was based on only seven breast cancer cases and was consequently not statistically significant. Furthermore, because patients with anorexia nervosa form a highly selective group, it is difficult to generalize these results *(35)*. By contrast, obesity in adulthood, which is the result of high energy intake relative to low energy expenditure,

is associated with increased breast cancer risk in postmenopausal women and probably with decreased breast cancer risk in premenopausal women *(36)*. All of these human studies suggest an important role of energy balance in breast cancer etiology, although such a role is not straightforward.

Data on short-term, transient caloric restriction, in which animals were allowed to eat freely after the restriction, are limited *(8–13)*. However, in one report *(8)*, rats were calorie restricted for a short period of time after they were weaned and were then fed *ad libitum* for the rest of their lives. Compared with rats that were fed *ad libitum* throughout life, rats that were subjected to short-term caloric restriction had an increased risk of malignant cancer later in life. An absence of a decreased risk of cancer or an actual increased risk of cancer by short-term, transient caloric restriction was also reported in other rodent studies *(9–13)*, of which two *(10,13)* refer to induced mammary tumors and caloric restriction during tumor initiation and promotion.

We hypothesize that several endocrine systems may adapt to adverse circumstances existent during the maturation of the hypothalamic–pituitary axis and show an inadequate response to the period of abundance thereafter, ultimately leading to increased risk of breast cancer. We have shown that levels of circulating insulin-like growth factor-I are increased in postmenopausal women who were severely exposed to the 1944–1945 Dutch famine before age 20 years *(37)*. Levels of sex steroids in the urine also seemed to be increased in postmenopausal women who were exposed to the 1944–1945 Dutch famine in young adulthood, although these associations were seen only in nulliparous women *(31)*. High levels of insulin-like growth factor-I and sex steroids are both associated with increased breast cancer risk *(38,39)*.

In conclusion, our data do not support the hypothesis that short-term, transient caloric restriction—such as during the 1944–1945 Dutch famine—decreases subsequent breast cancer risk. Our data suggest that the risk of breast cancer is increased in women severely exposed to the Dutch famine at a young age.

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NOTES

Supported by Dutch Cancer Society grants UU-KC-85-13 and UU-2000-2314 (to P.A.H. van Noord).

We thank Bernard Slotboom and Bep Verkerk for processing and handling of data. We also gratefully acknowledge the support of the regional population-based screening organization Stichting Preventicon and of the various municipalities within the region that provided us with the vital status information from the random sample as well as the support of the Comprehensive Cancer Centre Middle Netherlands in the record linkage.

Manuscript received September 22, 2003; revised February 3, 2004; accepted February 10, 2004.