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Height, Weight, Weight Change, and Ovarian Cancer Risk in the Netherlands Cohort Study on Diet and Cancer

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Although many studies have been conducted to investigate the relation between anthropometry and the risk of ovarian cancer, their results have been inconsistent. The Netherlands Cohort Study on Diet and Cancer was initiated in 1986. A self-administered questionnaire on dietary habits and other risk factors for cancer was completed by 62,573 women. Follow-up for cancer was implemented by annual record linkages with the Netherlands Cancer Registry. After 7.3 years of follow-up, 172 incident cases of invasive epithelial ovarian cancer were available for analysis. Multivariate analysis yielded a rate ratio of ovarian cancer for women with adult height of more than 175 cm, compared with those with height of less than or equal to 160 cm, of 2.17 (95% confidence interval: 1.14, 4.13; p trend = 0.01). The rate ratio for women with a body mass index of more than 30 kg/m^2 was 1.69 (95% confidence interval: 1.00, 2.86), compared with women with a Quetelet index of less than 25 kg/m^2, with p trend = 0.06. Rate ratios for weight and body mass index at age 20 years were nonsignificantly increased in the intermediate categories. These data support a positive association between height (and to a lesser extent body mass) and ovarian cancer risk in this population of postmenopausal women.

body constitution; body height; body mass index; body weight; cohort studies; ovarian neoplasms

Abbreviations: CI, confidence interval; RR, rate ratio.

Obesity has been found to be an important risk factor for many cancers. In the European Union, 5 percent of all cancers have been attributed to excess weight (1). The evidence for a consistent association with obesity is strongest for breast, colorectal, endometrial, gallbladder, kidney, and prostate cancer (1, 2).

An American Cancer Society study linked obesity to increased risk of ovarian cancer (3, 4). This relation is plausible, because several clinical conditions (e.g., polycystic ovarian syndrome, infertility, and so on) have been linked to both obesity and ovarian cancer (5–9). However, the results of other epidemiologic studies evaluating the relation between obesity and ovarian cancer have been inconsistent. Comparing their results is difficult because different methods were used, some studies using a clinical diagnosis of obesity from medical discharge registries as the exposure variable (10, 11) and other studies comparing mean values or presenting only the results for the top exposure category compared with the reference category.

The results of hospital-based case-control studies have been heterogeneous (12–20). These studies might suffer from selection bias, however, because it cannot be excluded that obesity was overrepresented in the control group (21, 22). Almost all population-based case-control studies have reported a positive relation (although not always statistically significant) between body mass and ovarian cancer risk (22–34). Very few prospective studies have been conducted (3, 10, 11, 35–37). Most of them showed a small positive effect of body mass on the risk of ovarian cancer. Only two studies were able to control for confounding by other important risk factors (36, 37). The Iowa Women's Health Study cohort found the rate ratio of the highest category to be only very marginally elevated. Another anthropometric measurement, waist/hip ratio, was positively correlated with ovarian cancer (36). A recent nested case-control study within a multicenter cohort study observed an inverse association (37).

The number of studies evaluating the relation between height and ovarian cancer has been much smaller. Some

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case-control studies reported a greater average height among cases than among controls (13, 18), although the difference was not statistically significant. Some studies reported elevated rate ratios for the highest categories, although again the differences were not significant (31, 38, 39).

Considering the lack of evidence on this topic and the heterogeneity of the published results, we decided to study anthropometry in relation to ovarian cancer in a prospective cohort study, allowing adjustment for the main potential confounders. We therefore examined the association of height and (relative) weight with ovarian cancer in the Netherlands Cohort Study on Diet and Cancer, which provides information on many potential confounders. We also evaluated whether dynamic anthropometric measures, such as (relative) weight gain during adulthood, are predictors of ovarian cancer risk.

MATERIALS AND METHODS

The cohort

The Netherlands Cohort Study on Diet and Cancer started in September 1986 when 62,573 Dutch women aged 55–69 years were enrolled in the cohort. All women were presumed to be postmenopausal. At baseline, cohort members completed a self-administered questionnaire on usual dietary intake and potential confounders, such as reproductive history, anthropometry, smoking habits, education, use of hormones, and family history of cancer. Data processing and analysis in the Cohort Study are based on the case-cohort approach; the cases are enumerated for the entire cohort (numerator information on incidence rates), while the accumulated person-years of the entire cohort are estimated using a subcohort sample (providing the denominator information). Following this approach, a subcohort of 1,812 women (2.9 percent of the total cohort) was sampled randomly from the cohort after the baseline exposure measurement. The size of the subcohort was based on calculations that have been described more extensively in a previous publication (40). Prevalent cancer cases (other than skin cancer) were excluded from the subcohort, with the result that 1,716 women remained in this group. The subcohort has been followed up biennially by mail for vital status information. The vital status of subcohort members who did not respond to the letter was completed by contacting the municipal register. Incident cancer cases occurring in the entire cohort were identified by record linkage to the Netherlands Cancer Registry and the Netherlands Pathology Registry (PALGA). Further details on the design of the Netherlands Cohort Study on Diet and Cancer and the method of cancer follow-up can be found in previous publications (40, 41).

The present analysis is restricted to cancer incidence in the 7.3-year follow-up period from September 1986 to December 1993. The completeness of cancer follow-up was estimated to be at least 96 percent (42), and no subcohort members were lost to follow-up. After a follow-up period of 7.3 years, 202 incident, microscopically confirmed, primary ovarian carcinomas were detected. After the exclusion of nonepithelial tumors ($n = 14$) and borderline invasive tumors ($n = 2$), 186 cases remained available. Women in the subcohort who had reported at baseline to have undergone an oophorectomy ($n = 16$) were excluded, leaving 1,700 subcohort members for analysis.

Questionnaire data

Self-reported information on height (in cm) and weight (in kg) at baseline, as well as weight at age 20 years (in kg), was obtained from the questionnaire. Questionnaire data of all cases and subcohort members were key entered twice and processed in a manner blinded with respect to case/subcohort status to minimize observer bias in the coding and interpretation of data. The baseline body mass index and the body mass index at age 20 years were calculated using baseline weight and weight at age 20 years, respectively, divided by height at baseline squared (kg/m^2). Body mass index was classified into the categories recommended by the National Institutes of Health (43). Because very few women in the subcohort fell into the three highest National Institutes of Health categories (30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2), these categories were combined. The following categories were thus used for body mass index: normal (≤24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). The change in body mass index from age 20 years was calculated as the body mass index at baseline minus the body mass index at age 20 years.

Women with incomplete anthropometric data were excluded, leaving 172 cases and 1,636 subcohort members for analysis. The analysis of weight at age 20 years was based on 152 cases and 1,477 subcohort members with complete data.

Data analysis

The mean values of the anthropometric variables were compared between cases and subcohort members. Other factors were considered as confounders if they were associated with ovarian cancer risk, if they were clearly associated with the anthropometric variables, and if rate ratios changed by more than 10 percent after adjustment. The confounders considered were age (continuous), use of oral contraceptives (ever vs. never), parity (no children, one or two children, or three or more children), use of postmenopausal hormones (ever vs. never), hysterectomy (yes or no), and family history of breast and/or ovarian cancer (yes or no). Family history was considered positive if breast and/or ovarian cancer was reported in a first-degree relative, that is, mother, sister, or daughter.

Incidence rate ratios and corresponding 95 percent confidence intervals for ovarian cancer were estimated in the age-adjusted and multivariate case-cohort analyses with categorized and continuous anthropometric variables, using exponentially distributed failure time regression models (44) processed with the Stata statistical software package (Stata Corporation, College Station, Texas). Standard errors were estimated using the robust Hubert-White sandwich estimator to account for additional variance introduced by sampling from the cohort. This method is equivalent to the variance-covariance estimator presented by Barlow (45). Tests for dose-response trends in the risk of ovarian cancer were

TABLE 1. Anthropometric variables and potential confounders in ovarian cancer cases and subcohort members, Netherlands Cohort Study on Diet and Cancer, 1986–1993

	Cases (n = 172)		Subcohort members (n = 1,636)	
	Mean	Standard deviation	Mean	Standard deviation
Anthropometric variables				
Height at baseline (cm)	166.4	6.4	165.1	6.2
Weight at baseline (kg)	70.2	10.5	68.6	10.2
Body mass index at baseline (kg/m^2)	25.3	3.5	25.2	3.5
Weight at age 20 years (kg)*	59.0	7.1	58.5	7.9
Body mass index at age 20 years (kg/m^2)*	21.3	2.1	21.5	2.7
Potentially confounding variables				
Age at baseline (years)	62.1	4.3	61.5	4.3
Ever use of oral contraceptives (%)	16.6		24.8	
Parity (% ever having a liveborn child)	73.7		82.5	
Ever use of postmenopausal hormone therapy (%)	8.1		12.3	
Hysterectomy (%)	5.2		6.5	
Family history of breast and/or ovarian cancer (%)†	8.7		8.4	

* Based on 152 cases and 1,477 subcohort members.

† Family history was considered positive, when breast and/or ovarian cancer was reported in a first-degree relative, that is, mother, sister, or daughter.

assessed by fitting ordinal exposure variables as continuous terms and performing likelihood-ratio tests between regression models with and without these variables. Two-sided p values are reported throughout the paper. Because preclinical disease might influence weight, we repeated the analyses for weight and body mass after excluding cases occurring in the first year of follow-up.

RESULTS

A total of 172 cases with ovarian cancer were available for analysis with complete anthropometric data. Of these 172 cases, 35 percent had a histologic diagnosis of serous carcinoma, 12 percent had endometrioid carcinoma, 11 percent had mucinous carcinoma, and 4 percent had clear cell carcinoma, while 35 percent had a histologic diagnosis of adenocarcinoma not otherwise specified, and the histology of 2 percent was unspecified.

Table 1 lists the anthropometric variables for cases and subcohort members. The mean height and weight differed between cases and subcohort members, in that cases were both taller and heavier. The difference in body mass index between cases and subcohort members was not great. Cases were also somewhat heavier than subcohort members at age 20 years. A comparison of subcohort members whose information on weight at age 20 years was missing with those who did report their weight at age 20 years yielded no significant differences in mean height, baseline weight, and body mass index (data not shown).

Table 1 also shows some potentially confounding variables. Fewer cases than subcohort members reported ever having used oral contraceptives (16.6 percent vs. 24.8 percent), fewer cases had children (73.7 percent vs. 82.5 percent), and fewer cases reported using postmenopausal hormone therapy (8.1 percent vs. 12.3 percent). No major differences were observed between cases and subcohort members with respect to hysterectomy and family history of breast and/or ovarian cancer. Because use of oral contraceptives, parity, and use of postmenopausal hormone therapy were associated with the risk of ovarian cancer and changed the risk estimate of one or more anthropometric variables, these three variables were considered as confounders in the further multivariate analyses.

Table 2 shows age-adjusted and multivariate-adjusted rate ratios of ovarian cancer for height, baseline weight, and body mass index at baseline. Height was positively correlated with the risk of ovarian cancer in both the univariate and multivariate analyses (p trend = 0.01). Weight was also positively associated with the risk of ovarian cancer but not significantly so (p trend = 0.18). Women who were obese at baseline (body mass index, ≥30 kg/m^2) had an increased risk of ovarian cancer compared with women who had a normal body mass (rate ratio (RR) = 1.69, 95 percent confidence interval (CI): 1.00, 2.86; p trend = 0.06).

Rate ratios for weight and body mass index at age 20 years are shown in table 3. The intermediate weight category at age 20 years showed the highest rate ratio of 1.79 compared with the lowest category, although the difference was not statistically significant (95 percent CI: 0.86, 3.72). The rate ratio of the highest category was only marginally elevated (RR = 1.11, 95 percent CI: 0.53, 2.32). Results for body mass index at age 20 years were comparable: an elevated rate ratio in the intermediate category (RR = 1.50, 95 percent CI: 0.89,

TABLE 2. Rate ratios and 95% confidence intervals for ovarian cancer according to anthropometric variables, Netherlands Cohort Study on Diet and Cancer, 1986–1993

Anthropometric variables	Categorical mean	Age adjusted			Multivariate adjusted		
		No. of cases/ no. of person-years in subcohort	RR*	95% CI*	No. of cases/ no. of person-years in subcohort	RR†	95% CI
Height at baseline (cm)							
<160	155.7	28/1,977	1	Reference	23/1,905	1	Reference
160–164	161.9	36/3,050	0.83	0.50, 1.40	36/2,875	0.98	0.57, 1.70
165–169	166.8	47/3,770	0.89	0.55, 1.46	45/3,603	1.01	0.59, 1.71
170–174	171.4	39/1,957	1.45	0.87, 2.43	35/1,901	1.51	0.86, 2.65
≥175	176.7	22/820	1.98	1.09, 3.62	20/791	2.17	1.14, 4.13
			p trend = 0.01			*p* trend = 0.01	
Height continuous, 10-cm increments			1.45	1.11, 1.89		1.42	1.08, 1.87
Weight at baseline (kg)							
<65	58.6	51/4,151	1	Reference	47/4,008	1	Reference‡
65–69	66.6	36/2,234	1.31	0.83, 2.04	33/2,212	1.25	0.77, 2.03
70–74	71.4	31/2,180	1.16	0.73, 1.85	31/2,129	1.23	0.76, 1.99
75–79	76.2	24/1,317	1.49	0.89, 2.49	23/1,253	1.54	0.89, 2.65
≥80	85.8	30/1,712	1.43	0.89, 2.30	28/1,632	1.32	0.78, 2.25
			p trend = 0.10			*p* trend = 0.18	
Weight continuous, 10- kg increments			1.17	1.01, 1.35		1.16	0.98, 1.37
Body mass index (kg/m^2)							
≤24.9	22.6	86/6,232	1	Reference	78/6,023	1	Reference
25–29.9	27.0	65/4,306	1.09	0.78, 1.53	61/4,089	1.21	0.84, 1.73
≥30	32.6	21/1,056	1.45	0.87, 2.41	20/962	1.69	1.00, 2.86
			p trend = 0.20			*p* trend = 0.06	
Body mass index continuous, 8-kg/m^2 increments			1.11	0.78, 1.57		1.25	0.88, 1.78

* RR, rate ratio; CI, confidence interval.

† Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), and ever use of postmenopausal hormone therapy.

‡ Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), ever use of postmenopausal hormones, and height.

2.51) and a decreased risk in the highest category (RR = 0.79, 95 percent CI: 0.48, 1.32).

The results for change in weight and body mass index between age 20 years and baseline are shown in table 4. Weight change since age 20 years (adjusted for weight at age 20 years, height, and confounders) was positively associated with an increased risk, although the difference was not statistically significant. The rate ratio for women who had a weight gain of 25 kg or more was 1.72 (95 percent CI: 0.72, 4.10) compared with women who had no weight change (*p* trend = 0.10). Change in body mass (adjusted for body mass at age 20 years) was not associated with the risk of ovarian cancer (*p* trend = 0.64).

Rate ratios for weight and body mass after exclusion of cases in the first year are presented in table 5. The rate ratios for weight were lower than in the analysis with all cases. The *p* trend was 0.33. The rate ratios for body mass index were slightly lower than in the analysis with all cases. Women who had a body mass index of 30 kg/m^2 or higher had a rate ratio of 1.62 (95 percent CI: 0.94, 2.80) compared with women who had a body mass index lower than 25.

DISCUSSION

This cohort study, with a relatively large series of cases, found a significant positive association between self-reported height and ovarian cancer incidence after controlling for several potential confounders. A positive but nonsignificant association with ovarian cancer was observed for weight and body mass index at baseline. Weight and body mass index at age 20 years were not consistently associated with increased risk of ovarian cancer, nor was change in weight and body mass index between age 20 years and baseline.

These results from the Netherlands Cohort Study on Diet and Cancer are not likely to have been affected by selection or information bias. Selection bias is unlikely given the high

TABLE 3. Rate ratios and 95% confidence intervals for ovarian cancer according to anthropometric variables at age 20 years, Netherlands Cohort Study on Diet and Cancer, 1986–1993

Anthropometric variables	Categorical mean	Age adjusted			Multivariate adjusted		
		No. of cases/ no. of person-years in subcohort	RR*	95% CI*	No. of cases/ no. of person-years in subcohort	RR†	95% CI
Weight at age 20 years (kg)							
<49	46.3	10/1,132	1	Reference	10/1,088	1	Reference‡
50–54	51.2	24/2,076	1.33	0.62, 2.84	22/1,996	1.15	0.53, 2.48
55–59	56.7	39/2,066	2.17	1.06, 4.45	34/1,978	1.79	0.86, 3.72
60–64	61.0	49/2,900	1.93	0.96, 3.90	46/2,780	1.55	0.77, 3.13
≥65	69.3	30/2,312	1.51	0.72, 3.17	28/2,196	1.11	0.53, 2.32
			p trend = 0.19			*p* trend = 0.72	
Weight at 20 years continuous, 10-kg increments			1.09	0.91, 1.32		0.99	0.81, 1.21
Body mass index at age 20 years (kg/m^2)							
<20	18.4	43/3,043	1	Reference	40/2,941	1	Reference
20–20.9	20.5	29/1,453	1.39	0.84, 2.29	28/1,389	1.50	0.89, 2.51
21–22.9	22.0	50/3,236	1.09	0.71, 1.68	44/3,098	1.06	0.68, 1.67
≥23	24.8	30/2,753	0.78	0.48, 1.26	28/2,610	0.79	0.48, 1.32
			p trend = 0.29			*p* trend = 0.30	
Body mass index at 20 years continuous, 8-kg/m^2 increments			0.85	0.57, 1.27		0.85	0.56, 1.31

* RR, rate ratio; CI, confidence interval.

† Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), and ever use of postmenopausal hormone therapy.

‡ Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), ever use of postmenopausal hormones, and height.

level of follow-up of cases and subcohort person-years (42, 46). All of the anthropometric results were self-reported, however, and misclassification of exposure is a potential source of bias. Although several studies have reported high correlations ($r > 0.8$) between self-reported and measured anthropometric data (47–49), other publications reported that, despite high correlations, weight tends to be underestimated and height overestimated, thus leading to lower estimates of body mass (50, 51). Mean values for the self-reported height and weight, however, were comparable with those of a representative sample of Dutch women 50–69 years of age measured in 1986 (52). The mean measured height and weight of the latter group ($n = 3,377$) were 165.6 cm and 68.9 kg, respectively, compared with 165.1 cm and 68.6 kg for our subcohort of women from the Netherlands Cohort Study on Diet and Cancer. Weight at age 20 years was used to calculate body mass index at age 20 years, and misclassification might have occurred because weight at age 20 years is difficult to remember. However, misclassification is expected to be nondifferential, and therefore, a possible effect on the risk estimates tends toward zero. Data regarding weight (and body mass index) at age 20 years were missing for 12 percent and 10 percent of the cases and the subcohort members, respectively. Subcohort members with and without information regarding weight at age 20 years did not differ significantly in baseline anthropometric measures. We were able to control for confounding by the most important risk factors (7). However, all covariates were measured at baseline only, and it is conceivable that use of postmenopausal hormone therapy had changed since then.

Obesity may have hampered diagnostics, causing delay in diagnosis, which would lower the risk estimates in the highest weight category. It is also conceivable that preclinical disease causes weight loss and may confound an association with body weight (2).

The relation between height and the risk of ovarian cancer has been studied in a few case-control studies. Two of these studies reported that cases were slightly more than 1 cm taller than controls, although the difference was not statistically significant (13, 18). This difference is in exact agreement with the findings of the present study. Another case-control study, however, reported no difference in mean height between cases and controls (24). In Greece, women with a height of 165 cm or more had a risk of 1.8 (95 percent CI: 0.8, 3.9) compared with women with a height of 154 cm or less (38). A more recent study in the same geographic

TABLE 4. Rate ratios and 95% confidence intervals for ovarian cancer according to change in weight and change in body mass index between age 20 years and baseline, Netherlands Cohort Study on Diet and Cancer, 1986–1993

Anthropometric variables	Categorical mean	Age adjusted			Multivariate adjusted		
		No. of cases/ no. of person-years in subcohort	RR*	95% CI*	No. of cases/ no. of person-years in subcohort	RR†	95% CI
Weight change (kg)							
−34–<0	−6.7	16/1,277	0.95	0.47, 1.92	14/1,229	1.01	0.46, 2.23
0–4.9	2.4	19/1,452	1	Reference	15/1,394	1	Reference‡
5–9.9	6.8	32/2,228	1.11	0.61, 2.02	30/2,134	1.32	0.68, 2.54
10–14.9	11.6	33/2,252	1.19	0.65, 2.16	32/2,150	1.42	0.74, 2.72
15–19.9	16.5	24/1,515	1.29	0.68, 2.45	24/1,465	1.57	0.78, 3.15
20–24.9	21.6	14/1,019	1.17	0.56, 2.47	14/975	1.48	0.67, 3.26
≥25	30.7	14/743	1.73	0.79, 3.77	11/692	1.72	0.72, 4.10
			p trend = 0.14			*p* trend = 0.10	
Weight change continuous, 10-kg increments			1.13	0.95, 1.34		1.15	0.95, 1.39
Body mass index change (kg/m²)							
−13.4–<0	−2.4	18/1,339	1.03	0.54, 1.97	15/1,290	0.85	0.42, 1.73
0–1.9	1.2	28/1,966	1	Reference	25/1,886	1	Reference
2.0–3.9	3.1	38/2,493	1.02	0.61, 1.72	35/2,377	1.03	0.59, 1.80
4.0–5.9	4.9	29/2,137	0.91	0.53, 1.57	29/2,037	1.00	0.56, 1.76
6.0–7.9	6.9	22/1,368	1.06	0.57, 1.98	22/1,339	1.23	0.64, 2.36
8.0–9.9	8.8	10/701	1.01	0.46, 2.19	7/650	0.81	0.33, 1.97
≥10.0	12.3	7/480	0.98	0.40, 2.41	7/459	1.15	0.47, 2.84
			p trend = 0.93			*p* trend = 0.64	
Body mass index change continuous, 8- kg/m² increments			1.12	0.75, 1.66		1.28	0.86, 1.91

* RR, rate ratio; CI, confidence interval.

† Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), and ever use of postmenopausal hormone therapy.

‡ Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), ever use of postmenopausal hormones, and height.

location did show a much lower risk estimate: Women with a height of 165 cm or more had a rate ratio of 1.13 (95 percent CI: 0.67, 1.90) compared with women with a height of 159 cm or less (53). The observed difference in outcome might be explained by the different reference category, but also by cohort effects. Polychronopoulou et al. (53) did not exclude an effect of height and suggested that the increasing trend in ovarian cancer mortality in Greece could be caused in part by the dramatic increase in adult height in that country. Two case-control studies in China and Japan found nonsignificantly increased risk estimates for the highest category compared with the lowest: 1.3 (95 percent CI: 0.6, 3.1) and 1.4 (95 percent CI: 0.6, 3.0), respectively (31, 39). Only one prospective study has provided results on the relation between height and risk of ovarian cancer (54). The power of this study (only nine cases) was too small to yield any meaningful results. A recent multicenter nested case-control study reported some evidence of a direct association of ovarian cancer and height in cancers diagnosed before the age of 55 years (37), but precise rate ratios were not published.

Height has been associated with several types of cancer, especially breast cancer (55). Height as such does not cause cancer but probably acts as a biomarker for some other exposure (55). Suggested hypotheses include genetic factors, calorie restriction in early life, and an increased exposure to sex and growth hormones. Several investigators have noted that height-cancer associations are strongest in birth cohorts exposed to periods of food shortages during prepubertal growth (56–59). This may also be a possible clue to the apparent discrepancy in outcomes between the two Greek studies (38, 53). Women in the Dutch cohort of the Netherlands Cohort Study on Diet and Cancer experienced the economic crisis of the 1930s in their youth, as well as the German occupation during the Second World War, including particularly the famine in the winter of 1944 (60). Food restriction during youth may restrict serum levels of insulin-like growth factor I (61, 62), which inhibits apoptosis of damaged cells and stimulates cell turnover and cell proliferation (63, 64). The link between height and increased risk of ovarian cancer therefore does not seem implausible, and

TABLE 5. Rate ratios and 95% confidence intervals for ovarian cancer according to anthropometric variables at baseline after exclusion of cases diagnosed during the first year of follow-up, Netherlands Cohort Study on Diet and Cancer, 1986–1993

Anthropometric variables	Categorical mean	Age adjusted			Multivariate adjusted		
		No. of cases/ no. of person-years in subcohort	RR*	95% CI*	No. of cases/ no. of person-years in subcohort	RR†	95% CI
Weight at baseline (kg)							
<65	58.6	50/4,150	1	Reference	44/3,963	1	Reference‡
65–69	66.6	33/2,233	1.22	0.77, 1.94	30/2,174	1.16	0.70, 1.91
70–74	71.4	30/2,179	1.15	0.72, 1.84	30/2,106	1.21	0.74, 1.97
75–79	76.2	22/1,317	1.39	0.82, 2.36	21/1,238	1.43	0.81, 2.51
≥80	85.8	25/1,711	1.21	0.73, 2.01	24/1,588	1.19	0.69, 2.07
			p trend = 0.31			*p* trend = 0.33	
Weight continuous, 10-kg increments			1.12	0.96, 1.31		1.13	0.95, 1.34
Body mass index (kg/m²)							
≤24.9	22.6	82/6,229	1	Reference	74/6,020	1	Reference
25–29.9	27.0	60/4,305	1.06	0.75, 1.50	57/4,087	1.20	0.83, 1.73
≥30	32.6	18/1,056	1.30	0.76, 2.23	18/961	1.62	0.94, 2.80
			p trend = 0.40			*p* trend = 0.09	
Body mass index continuous, 8-kg/m² increments			1.00	0.95, 1.05		1.02	0.98, 1.07

* RR, rate ratio; CI, confidence interval.

† Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), and ever use of postmenopausal hormone therapy.

‡ Rate ratios adjusted for age at baseline, ever use of oral contraceptives, parity (no children, 1–2 children, or ≥3 children), ever use of postmenopausal hormones, and height.

insulin-like growth factor I must be considered as one of the factors involved in this relation.

Although several studies have published results on the relation between weight or body mass and the risk of ovarian cancer, interpretation is hampered by differences in methodology and presentation of the results. A study by the American Cancer Society was the first to publish results on the relation between anthropometric data and the risk of ovarian cancer (3, 4). Women whose weight was 40 percent higher than the mean (adjusted for age and height) had a rate ratio of 1.63 compared with women of average weight. Several case-control studies have reported a higher average weight or body mass index among cases than among controls (18, 29) or reported a higher prevalence or increased rate ratio for excess (relative) weight or clinical obesity among cases (12, 23, 25, 65). On the other hand, several other case-control studies have reported lower average weight for cases than for controls (13, 17, 18) or decreased rate ratios for the highest category of (relative) weight (14, 15, 19, 66, 67).

As noted by Whittemore et al. (68) and Purdie et al. (22), all these studies that found a negative or no association used hospital-based controls (13–20). Selection bias has been suggested as an explanation for the lack of association or the negative associations found in hospital-based case-control studies (21, 22). It was suggested that obese persons are overrepresented in a series of hospital controls. Most case-control studies, however, including almost all population-based case-control studies, published a positive, albeit moderate association between weight and/or body mass index and the risk of ovarian cancer (22, 24, 26–28, 30, 31, 34). A few case-control studies reported no association or a very small association (odds ratio ≤1.1): Two of these were hospital based (16, 20), and two were population based (32, 39). A recent systematic review concluded that there is a small-to-moderate positive relation between high body mass index and the occurrence of ovarian cancer (22). Overall, the hospital-based case-control studies observed no relation (summary RR = 1.1, 95 percent CI: 0.9, 1.2), while the population-based case-control studies yielded positive relations (summary RR = 1.4, 95 percent CI: 1.2, 1.6) (22). Since the study by the American Cancer Society, only a few prospective cohort studies have published results with respect to the relation between weight or body mass index and ovarian cancer risk. Törnberg and Carstensen (35) analyzed the risk of increasing body mass index and found a positive association in women below the age of 55 years (RR = 1.66 for body mass index of 28 or higher compared with body mass index below 22) but no association in women who were more than 55 years of age. These rate ratios were not adjusted for the major potential confounders. Moller et al. (10) and Wolk et al. (11) studied the incidence of ovarian cancer in women who had been recorded in the hospital discharge registry with a diagnosis of obesity (*International Classification of Diseases*, Ninth Revision, code 277) and compared the observed incidence rates with the expected rates based on the general population. Moller et al. found a small and statisti-

cally nonsignificant risk (RR = 1.1, 95 percent CI: 0.8, 1.4), while Wolk et al. found a rate ratio of 1.2 (95 percent CI: 1.1, 1.5). These studies could not adjust for confounders. Mink et al. (36) were able to adjust for confounders and found no statistically significant association for women who had a body mass index higher than 29.5 compared with those who had a body mass index lower than 23.5 (RR = 1.1, 95 percent CI: 0.64, 1.93). The waist/hip ratio, however, was significantly increased in the highest quartile compared with the lowest quartile (RR = 1.92, 95 percent CI: 1.03, 3.60). Overall, Purdie et al. (22) calculated a summary rate ratio of 1.2 (95 percent CI: 1.1, 1.3) for the cohort studies. These results are in agreement with our findings.

The review by Purdie et al. did not include the study by Lukanova et al. (37). In a multicenter nested case-control study with 122 cases, they observed an inverse association between increasing weight and risk of ovarian cancer. The highest body mass index category (≥28.4 kg/m^2) had a multivariate-adjusted relative risk of 0.46 compared with women who had a body mass below 23.1. The age at recruitment in this multicenter cohort was lower than in our cohort, and the mean age at diagnosis was 59.4 years (compared with 62.1 years in our study). This means that a considerable proportion of the cases must have been premenopausal at diagnosis, and that the measured weight and body mass reflected mainly premenopausal exposure.

As regards the etiology of ovarian cancer, several hypotheses have been put forward. Fathalla (69) and Casagrande et al. (23) have proposed the "incessant ovulation" hypothesis, assuming that ovulation causes trauma to the ovarian epithelium and that the higher the number of ovulations the greater the risk of ovarian cancer. Cramer and Welch (70) suggested that excessive amounts of gonadotropins stimulate ovarian carcinogenesis. A more recent hypothesis by Risch (71) suggests that high serum levels of androgens increase the risk of ovarian cancer, while progestagens protect against ovarian cancer.

Obesity has multiple effects on the hormonal status of pre- and postmenopausal women. In premenopausal women, it lowers sex hormone-binding globulin and increases the serum levels of insulin-like growth factor I, but it does not influence levels of estrogens and androgens significantly, because the ovaries produce more steroids than the peripheral fat tissue (2, 72). In postmenopausal women, the levels of estrogens and androgens are increased because the main production is by peripheral fat tissue, while serum levels of free progestagens are decreased (2). According to the hypothesis by Risch this would predict a positive relation between weight or body mass and the risk of ovarian cancer in the postmenopausal period.

Only a limited number of case-control studies have considered the influence of weight (or body mass index) at a young adult age. Purdie et al. (22) reported little deviation from zero across the range of body mass index at age 20 years. Farrow et al. (26) reported an increasing trend for body mass index according to categories at age 30 years ($p < 0.05$). Mori et al. (31) reported an increased risk for women heavier than 55 kg compared with women lighter than 45 kg (odds ratio = 1.52, 95 percent CI: 0.78, 2.96). Our study found no consistent increasing trend. The rate ratio was nonsignificantly decreased in the highest category of body mass index at age 20 years, while the rate ratio in the second category was nonsignificantly increased. Purdie et al. (22) reported a significantly elevated risk for the highest category of change in weight since age 20 years. This observation was not confirmed in our study. Clinical obesity (>30 kg/m^2) in the fertile age is known to increase the frequency of anovulatory menstrual cycles (73). The Nurses' Health Study found the risk of ovulatory infertility to be increased in women with a body mass index less than 20 or greater than 24 (74). According to the theory by Fathalla (69), fewer ovulatory cycles would decrease the risk of ovarian cancer. As regards weight and body mass index at age 20 years, we observed that the risks were smallest in the lowest and the highest categories (although the differences were not statistically significant). According to Fathalla's theory, this is in agreement with the results of the Nurses' Health Study.

The findings of the present prospective study support a positive association between height (and to a lesser extent weight) and ovarian cancer risk in this population of postmenopausal women. Confirmation of these results in other well-designed prospective studies is warranted, while the relation with body mass at age 20 years and weight gain since then needs further research.

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