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Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

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ABSTRACT

BACKGROUND

The influence of excess body weight on the risk of death from cancer has not been fully characterized.

METHODS

In a prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, there were 57,145 deaths from cancer during 16 years of follow-up. We examined the relation in men and women between the body-mass index in 1982 and the risk of death from all cancers and from cancers at individual sites, while controlling for other risk factors in multivariate proportional-hazards models. We calculated the proportion of all deaths from cancer that was attributable to overweight and obesity in the U.S. population on the basis of risk estimates from the current study and national estimates of the prevalence of overweight and obesity in the U.S. adult population.

RESULTS

The heaviest members of this cohort (those with a body-mass index [the weight in kilograms divided by the square of the height in meters] of at least 40) had death rates from all cancers combined that were 52 percent higher (for men) and 62 percent higher (for women) than the rates in men and women of normal weight. For men, the relative risk of death was 1.52 (95 percent confidence interval, 1.13 to 2.05); for women, the relative risk was 1.62 (95 percent confidence interval, 1.40 to 1.87). In both men and women, body-mass index was also significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for death due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher body-mass-index values were observed for death from cancers of the stomach and prostate in men and for death from cancers of the breast, uterus, cervix, and ovary in women. On the basis of associations observed in this study, we estimate that current patterns of overweight and obesity in the United States could account for 14 percent of all deaths from cancer in men and 20 percent of those in women.

CONCLUSIONS

Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites.

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THE RELATIONS BETWEEN EXCESS BODY weight and mortality, not only from all causes but also from cardiovascular disease, are well established.¹⁻⁶ Although we have known for some time that excess weight is also an important factor in death from cancer,⁷ our knowledge of the magnitude of the relation, both for all cancers and for cancers at individual sites, and the public health effect of excess weight in terms of total mortality from cancer is limited.

Previous studies have consistently shown associations between adiposity and increased risk of cancers of the endometrium, kidney, gallbladder (in women), breast (in postmenopausal women), and colon (particularly in men).⁸⁻¹² Adenocarcinoma of the esophagus has been linked to obesity.^{11,13,14} Data on cancers of the pancreas, prostate, liver, cervix, and ovary and on hematopoietic cancers are scarce or inconsistent.^{7-11,15-17} The lack of consistency may be attributable to the limited number of studies (especially those with prospective cohorts), the limited range and variable categorization of overweight and obesity among studies, bias introduced by reverse causality with respect to smoking-related cancers, and possibly real differences between the effects of overweight and obesity on the incidence of cancer and on the rates of death from some cancers.^{18,19}

We conducted a prospective investigation in a large cohort of U.S. men and women to determine the relations between body-mass index (the weight in kilograms divided by the square of the height in meters) and the risk of death from cancer at specific sites. This cohort has been used previously to examine the association of body-mass index and death from any cause.⁵

METHODS

STUDY POPULATION

The men and women in this study were selected from the 1,184,617 participants in the Cancer Prevention Study II, a prospective mortality study begun by the American Cancer Society in 1982.^{20,21} The participants were identified and enrolled by more than 77,000 volunteers in all 50 states, the District of Columbia, and Puerto Rico. Families were enrolled if at least one household member was 45 years of age or older and all enrolled members were 30 years of age or older. The average age of the participants at enrollment was 57 years. In 1982 they completed a confidential mailed questionnaire that in-

cluded personal identifiers and elicited information on demographic characteristics, personal and family history of cancer and other diseases, and various behavioral, environmental, occupational, and dietary exposures.

Over 99 percent of deaths that occurred from the month of enrollment until September 1988 were ascertained by means of personal inquiries made by volunteers in September 1984, 1986, and 1988.²² Approximately 93 percent of all deaths occurring after September 1988 were ascertained by linkage with the National Death Index.²² By December 31, 1998, 24.0 percent of the participants had died, 75.8 percent were still living, and 0.2 percent were dropped from follow-up on September 1, 1988, because of insufficient data for linkage with the National Death Index. Death certificates or multiple cause-of-death codes were obtained for 98.8 percent of all known deaths.

In the base-line questionnaire, the participants were asked their current weight, weight one year previously, and height (without shoes). We excluded from the analysis participants whose values for height or weight were missing, whose weight one year before the interview was unknown, or who had lost more than 10 lb (4.5 kg) in the previous year; 65,436 men and 91,282 women were excluded for these reasons. We also excluded participants with below-normal weight according to World Health Organization guidelines²³ as indicated by a body-mass index of less than 18.5 (3393 men and 15,769 women). In addition, we excluded participants who had cancer (other than nonmelanoma skin cancer) at base line (20,839 men and 47,120 women) and those with missing information on race or smoking history (14,086 men and 26,639 women). The eligible participants for the current analysis included 404,576 men and 495,477 women. After 16 years of follow-up, there were a total of 32,303 deaths from cancer in men and 24,842 deaths from cancer in women in this population.

From the final population of 900,053 participants, we defined a subgroup of those who had never smoked (107,030 men and 276,564 women). Within this subgroup, there were a total of 5314 deaths from cancer among men and 11,648 among women. This subgroup provided us with an opportunity to evaluate whether the association between body-mass index and mortality was subject to residual confounding by smoking status for smoking-related cancers.

BODY-MASS INDEX

The body-mass index, a measure of adiposity, was categorized as follows: 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, 35.0 to 39.9, and 40.0 or more. These categories correspond to those proposed by the World Health Organization²³ for “normal range,” “grade 1 overweight,” “grade 2 overweight” (30.0 to 39.9), and “grade 3 overweight,” respectively. For many analyses, especially for cancers in specific sites and among participants who had never smoked, the upper categories of body-mass index were combined, because of the small numbers. In our analyses and discussion, we refer to the range of 25.0 to 29.9 as corresponding to “overweight” and to values of 30.0 or more as corresponding to “obesity.”

In all primary analyses, the body-mass index category of 18.5 to 24.9 (“normal range”) was considered the reference group. We also conducted analyses in which we divided this group into two categories of 18.5 to 22.9 and 23.0 to 24.9 and considered the lower category to be the reference group.

MORTALITY END POINTS

The end points in our analyses were deaths from all cancers (codes 140.0 to 195.8 and 199.0 to 208.9 of the *International Classification of Diseases, Ninth Revision* [ICD-9])²⁴ and from cancers at selected sites. Specific cancers accounting for at least 150 deaths in men and 150 deaths in women included esophageal cancer (ICD-9 codes 150.0 to 150.9), stomach cancer (151.0 to 151.9), colorectal cancer (153.0 to 154.8), liver cancer (155.0 to 155.2), gallbladder cancer (156.0 to 156.9), pancreatic cancer (157.0 to 157.9), lung cancer (162.0 to 162.9), melanoma (172.0 to 172.9), breast cancer in women (174.0 to 174.9), cancer of the corpus and uterus, not otherwise specified (179 and 182.0 to 182.8), cervical cancer (180.0 to 180.9), ovarian cancer (183.0 to 183.9), prostate cancer (185), bladder cancer (188.0 to 188.9), kidney cancer (189.0 to 189.9), brain cancer (191.0 to 191.9), non-Hodgkin’s lymphoma (202.0 to 202.9), multiple myeloma (203.0 to 203.8), and leukemia (204.0 to 208.9). All other specific cancers that contributed to total deaths from cancer but that caused fewer than 150 deaths or were coded as unspecified (199.0 to 199.1) were analyzed as a separate category of “other” cancers. Approximately 11 percent of cancers in both men and women fell into the “other” category. Of these, 45 percent had a specific (coded) site and caused fewer than 150 deaths and 55 percent had a site

that was coded as unspecified. Data regarding cancer subsites or histologic findings were not available.

INFORMATION ON COVARIATES

Potential confounders included in data analyses were age (in single years), race (white, black, or other), smoking status (never smoked, formerly smoked, or currently smokes, with three categories of cigarettes smoked per day: 0 to 19, 20, and more than 20), education (less than high school, high-school graduate, some college, or college graduate), physical activity (none, slight, moderate, or heavy), alcohol use (none, less than one drink per day, one drink per day, or two or more drinks per day), marital status (not married or married), current aspirin use (use or nonuse), a crude index of fat consumption (estimated grams per week for 20 food items, with the participants divided into three roughly equal groups),²⁵ and vegetable consumption (the frequency per week of consumption of nine vegetables — not including potatoes — with participants divided into three roughly equal groups), and status with respect to estrogen-replacement therapy in women (never used, currently used, or formerly used).

STATISTICAL ANALYSIS

Age-adjusted death rates were calculated for each category of body-mass index and were directly standardized to the age distribution of the entire male or female study population. Relative risks (the age-adjusted death rate in a specific body-mass-index category divided by the corresponding rate in the reference category [18.50 to 24.99]) were computed; the 95 percent confidence intervals used approximate variance formulas.^{26,27}

We also used Cox proportional-hazards modeling²⁸ to compute relative risks and to adjust for other potential risk factors reported at base line. The Cox models were stratified according to age at enrollment by the inclusion of age (in single years) in the strata statement of the Cox model. The relative risks we report are from the multivariate Cox models, unless otherwise noted. Tests of linear trend were performed by scoring the categories of body-mass index, entering the score as a continuous term in the regression model, and testing the significance of the term by the Wald chi-square test.²⁹

We present results for all cancers combined and for cancer at each site on the basis of analyses of the total populations of men and women. For most in-

Table 1. Mortality from Cancer According to Body-Mass Index among U.S. Men in the Cancer Prevention Study II, 1982 through 1998.*

Type of Cancer	Body-Mass Index†					P for Trend
	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	
All cancers						
No. of deaths	13,855	15,372	2683	350	43	
Death rate‡	578.30	546.21	636.30	738.69	841.62	
RR (95% CI)§	1.00	0.97 (0.94–0.99)	1.09 (1.05–1.14)	1.20 (1.08–1.34)	1.52 (1.13–2.05)	0.001
All cancers						
No. of deaths	13,855	15,372	2683	393¶		
Death rate‡	578.30	546.21	636.30	749.86¶		
RR (95% CI)§	1.00	0.97 (0.94–0.99)	1.09 (1.05–1.14)	1.23 (1.11–1.36)¶		0.002
Esophageal cancer						
No. of deaths	329	452	81	14		
Death rate‡	13.97	15.74	18.07	24.18		
RR (95% CI)§	1.00	1.15 (0.99–1.32)	1.28 (1.00–1.63)	1.63 (0.95–2.80)		0.008
Stomach cancer						
No. of deaths	388	455	84	18		
Death rate‡	16.24	16.09	20.34	33.99		
RR (95% CI)§	1.00	1.01 (0.88–1.16)	1.20 (0.94–1.52)	1.94 (1.21–3.13)		0.03
Colorectal cancer						
No. of deaths	1,292	1,811	337	54		
Death rate‡	53.51	64.43	79.50	101.25		
RR (95% CI)§	1.00	1.20 (1.12–1.30)	1.47 (1.30–1.66)	1.84 (1.39–2.41)		<0.001
Liver cancer						
No. of deaths	222	296	78	24		
Death rate‡	9.24	10.49	19.22	47.80		
RR (95% CI)§	1.00	1.13 (0.94–1.34)	1.90 (1.46–2.47)	4.52 (2.94–6.94)		<0.001
Gallbladder cancer						
No. of deaths	66	94	20			
Death rate‡	2.68	3.37	5.16			
RR (95% CI)§	1.00	1.34 (0.97–1.84)	1.76 (1.06–2.94)			0.02
Pancreatic cancer						
No. of deaths	740	961	182	25		
Death rate‡	31.07	33.98	42.20	48.80		
RR (95% CI)§	1.00	1.13 (1.03–1.25)	1.41 (1.19–1.66)	1.49 (0.99–2.22)		<0.001
Lung cancer						
No. of deaths	4,885	4,281	681	78		
Death rate‡	206.69	150.11	156.53	149.63		
RR (95% CI)§	1.00	0.78 (0.75–0.82)	0.79 (0.73–0.86)	0.67 (0.54–0.84)		<0.001
Melanoma						
No. of deaths	238	279	43			
Death rate‡	10.02	9.77	8.09			
RR (95% CI)§	1.00	0.95 (0.80–1.13)	0.85 (0.61–1.18)			0.32
Prostate cancer						
No. of deaths	1,681	1,971	311	41		
Death rate‡	67.36	73.02	83.00	87.35		
RR (95% CI)§	1.00	1.08 (1.01–1.15)	1.20 (1.06–1.36)	1.34 (0.98–1.83)		<0.001
Bladder cancer						
No. of deaths	375	421	76			
Death rate‡	15.19	15.47	16.69			
RR (95% CI)§	1.00	1.03 (0.89–1.18)	1.14 (0.88–1.46)			0.36
Kidney cancer						
No. of deaths	305	437	81	14		
Death rate‡	12.83	15.25	18.50	24.84		
RR (95% CI)§	1.00	1.18 (1.02–1.37)	1.36 (1.06–1.74)	1.70 (0.99–2.92)		0.002

Table 1. (Continued.)

Type of Cancer	Body-Mass Index†					P for Trend
	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	
Brain cancer						
No. of deaths	370	461	68			
Death rate‡	15.98	15.86	12.76			
RR (95% CI)§	1.00	0.98 (0.85–1.13)	0.79 (0.61–1.03)			0.14
Non-Hodgkin's lymphoma						
No. of deaths	518	672	147	18		
Death rate‡	21.51	24.04	35.25	33.22		
RR (95% CI)§	1.00	1.08 (0.96–1.21)	1.56 (1.29–1.87)	1.49 (0.93–2.39)		<0.001
Multiple myeloma						
No. of deaths	259	368	70	11		
Death rate‡	10.77	13.18	16.88	20.62		
RR (95% CI)§	1.00	1.18 (1.01–1.39)	1.44 (1.10–1.89)	1.71 (0.93–3.14)		0.002
Leukemia						
No. of deaths	546	720	128	20		
Death rate‡	22.51	25.60	30.40	40.52		
RR (95% CI)§	1.00	1.14 (1.02–1.28)	1.37 (1.13–1.67)	1.70 (1.08–2.66)		<0.001
All other cancers						
No. of deaths	1,641	1,693	320	52		
Death rate‡	68.72	59.81	73.29	101.88		
RR (95% CI)§	1.00	0.89 (0.83–0.95)	1.06 (0.94–1.20)	1.29 (0.98–1.71)		0.98

* Participants with any of the following features at study entry were excluded: missing data on height or current weight; unknown weight one year before entry; weight loss at least 10 lb (4.5 kg) in the previous year; body-mass index under 18.50; existing cancer (other than nonmelanoma skin cancer); unknown race or missing data; and missing data on smoking status. RR denotes relative risk, and CI confidence interval.

† The highest body-mass-index category examined varies for cancer at different sites; higher categories have been combined when necessary because of small numbers.

‡ The rate per 100,000 is given, standardized to the age distribution of men in the Cancer Prevention Study II.

§ The Cox proportional-hazards model was adjusted for age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, fat consumption, and vegetable consumption.

¶ This value is for the 35.0–39.9 and ≥40.0 groups combined and is provided to facilitate comparison with the types of cancer.

dividual cancer sites, the association of body-mass index and mortality was similar whether the analysis was based on the total population or on the population of those who had never smoked. However, for several cancers known to be related to smoking, the association between body-mass index and mortality was substantially different in the total population and the population of those who had never smoked. For these cancers (in men, all cancers, lung cancer, esophageal cancer, pancreatic cancer, and other cancers; in women, all cancers, lung cancer, esophageal cancer, and other cancers), the results from the population of those who had never smoked are also presented.

Because weight is a modifiable risk factor, we calculated the population attributable fraction (also termed population attributable risk, population attributable-risk proportion, and excess fraction),³⁰

an estimate of the proportion of all cancer deaths in the United States that might be avoided if the adult population maintained a body-mass index in the normal range. We used methods derived by Walter³¹ and presented by Kleinbaum et al.³² for a multiple-category exposure. In this analysis, calculations were based on the multivariate-adjusted relative risks for the total population in the Cancer Prevention Study II and for the population of those in that study who had never smoked and on prevalence estimates of overweight and obesity in U.S. men and women 50 to 69 years of age from the National Health and Nutrition Examination Survey for 1999–2000.³³ This calculation assumes that the relative-risk estimates associated with overweight and obesity that were observed in the current study were causal and are generalizable to the U.S. population.

Table 2. Mortality from Cancer According to Body-Mass Index among U.S. Women in the Cancer Prevention Study II, 1982 through 1998.*

Type of Cancer	Body-Mass Index†					P for Trend
	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	
All cancers						
No. of deaths	14,779	7107	2254	517	185	
Death rate‡	329.30	339.75	382.62	419.59	522.51	
RR (95% CI)§	1.00	1.08 (1.05–1.11)	1.23 (1.18–1.29)	1.32 (1.20–1.44)	1.62 (1.40–1.87)	<0.001
Esophageal cancer						
No. of deaths	112	56	21			
Death rate‡	2.56	2.68	2.90			
RR (95% CI)§	1.00	1.20 (0.86–1.66)	1.39 (0.86–2.25)			0.13
Stomach cancer						
No. of deaths	304	134	57	13		
Death rate‡	6.87	6.37	9.88	9.85		
RR (95% CI)§	1.00	0.89 (0.72–1.09)	1.30 (0.97–1.74)	1.08 (0.61–1.89)		0.46
Colorectal cancer						
No. of deaths	1,706	906	312	67	21	
Death rate‡	38.67	43.28	53.81	56.14	63.11	
RR (95% CI)§	1.00	1.10 (1.01–1.19)	1.33 (1.17–1.51)	1.36 (1.06–1.74)	1.46 (0.94–2.24)	<0.001
Liver cancer						
No. of deaths	200	96	37	12		
Death rate‡	4.53	4.54	6.34	7.52		
RR (95% CI)§	1.00	1.02 (0.80–1.31)	1.40 (0.97–2.00)	1.68 (0.93–3.05)		0.04
Gallbladder cancer						
No. of deaths	159	86	59			
Death rate‡	3.57	4.15	7.79			
RR (95% CI)§	1.00	1.12 (0.86–1.47)	2.13 (1.56–2.90)			<0.001
Pancreatic cancer						
No. of deaths	952	490	154	35	19	
Death rate‡	21.47	23.24	26.20	27.70	51.65	
RR (95% CI)§	1.00	1.11 (1.00–1.24)	1.28 (1.07–1.52)	1.41 (1.01–1.99)	2.76 (1.74–4.36)	<0.001
Lung cancer						
No. of deaths	3,693	1278	305	54	19	
Death rate‡	81.48	60.80	51.23	43.67	52.64	
RR (95% CI)§	1.00	0.88 (0.83–0.94)	0.82 (0.72–0.92)	0.66 (0.50–0.86)	0.81 (0.52–1.28)	<0.001
Melanoma						
No. of deaths	166	61	28			
Death rate‡	3.65	2.96	3.63			
RR (95% CI)§	1.00	0.85 (0.63–1.14)	1.10 (0.73–1.66)			0.95
Breast cancer¶						
No. of deaths	1,446	908	309	68	24	
Death rate‡	39.10	51.13	60.65	67.56	84.86	
RR (95% CI)§	1.00	1.34 (1.23–1.46)	1.63 (1.44–1.85)	1.70 (1.33–2.17)	2.12 (1.41–3.19)	<0.001
Cancer of the corpus and uterus, not otherwise specified						
No. of deaths	333	225	105	25	16	
Death rate‡	10.68	15.68	26.05	30.16	60.83	
RR (95% CI)§	1.00	1.50 (1.26–1.78)	2.53 (2.02–3.18)	2.77 (1.83–4.18)	6.25 (3.75–10.42)	<0.001
Cervical cancer						
No. of deaths	80	54	16	14		
Death rate‡	1.73	2.63	2.73	7.81		
RR (95% CI)§	1.00	1.38 (0.97–1.96)	1.23 (0.71–2.13)	3.20 (1.77–5.78)		0.001

Table 2. (Continued.)

Type of Cancer	Body-Mass Index†					P for Trend
	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	
Ovarian cancer**						
No. of deaths	873	437	126	49		
Death rate‡	27.88	31.44	31.85	44.49		
RR (95% CI)§	1.00	1.15 (1.02–1.29)	1.16 (0.96–1.40)	1.51 (1.12–2.02)		0.001
Bladder cancer						
No. of deaths	180	83	34			
Death rate‡	4.21	3.93	4.82			
RR (95% CI)§	1.00	1.02 (0.78–1.33)	1.34 (0.91–1.95)			0.21
Kidney cancer						
No. of deaths	243	153	55	12	10	
Death rate‡	5.43	7.35	9.24	9.56	30.14	
RR (95% CI)§	1.00	1.33 (1.08–1.63)	1.66 (1.23–2.24)	1.70 (0.94–3.05)	4.75 (2.50–9.04)	<0.001
Brain cancer						
No. of deaths	467	213	64	12		
Death rate‡	10.26	10.27	10.68	6.35		
RR (95% CI)§	1.00	1.02 (0.87–1.21)	1.10 (0.84–1.44)	0.74 (0.42–1.32)		0.96
Non-Hodgkin's lymphoma						
No. of deaths	576	327	88	38		
Death rate‡	13.02	15.48	14.99	24.09		
RR (95% CI)§	1.00	1.22 (1.06–1.40)	1.20 (0.95–1.51)	1.95 (1.39–2.72)		<0.001
Multiple myeloma						
No. of deaths	341	187	72	20		
Death rate‡	7.71	8.87	12.28	12.88		
RR (95% CI)§	1.00	1.12 (0.93–1.34)	1.47 (1.13–1.91)	1.44 (0.91–2.28)		0.004
Leukemia						
No. of deaths	574	282	83	18		
Death rate‡	13.05	13.53	14.17	12.72		
RR (95% CI)§	1.00	1.05 (0.91–1.21)	1.12 (0.89–1.42)	0.93 (0.58–1.49)		0.53
All other cancers						
No. of deaths	1,582	801	239	61	22	
Death rate‡	35.70	38.15	40.61	51.99	69.19	
RR (95% CI)§	1.00	1.11 (1.02–1.21)	1.20 (1.05–1.38)	1.47 (1.13–1.90)	1.83 (1.20–2.80)	<0.001

* Participants with any of the following features at study entry were excluded: missing data on height or current weight; unknown weight one year before entry; weight loss of at least 10 lb (4.5 kg) in the previous year; body-mass index under 18.50; existing cancer (other than nonmelanoma skin cancer); unknown race or missing data; and missing data on smoking status. RR denotes relative risk, and CI confidence interval.

† The highest body-mass-index category examined varies for different cancer sites; upper categories have been combined when necessary because of small numbers.

‡ The rate per 100,000 is given, standardized to the age distribution of women in the Cancer Prevention Study II.

§ The Cox proportional-hazards model was adjusted for age, education, smoking status and number of cigarettes smoked, physical activity, alcohol use, marital status, race, aspirin use, estrogen-replacement therapy, fat consumption, and vegetable consumption.

¶ Women who were premenopausal or perimenopausal or whose menopausal status was unknown were excluded (147,583 women, with 871 deaths).

|| Women who had a hysterectomy were excluded (130,717 women, 25 deaths).

**Women who had either a hysterectomy or ovarian surgery were excluded (141,924 women, 389 deaths).

RESULTS

BODY-MASS INDEX AND MORTALITY FROM CANCER IN THE TOTAL POPULATION OF MEN AND WOMEN

The numbers of deaths among men were sufficient to permit only the death rates from all cancers to be

examined separately for the two highest body-mass-index categories of 35.0 to 39.9 and 40.0 or more. The relative risks of death for these categories, as compared with the group of men of normal weight (body-mass index, 18.5 to 24.9), were 1.20 (95 percent confidence interval, 1.08 to 1.34) and 1.52 (95 percent confidence interval, 1.13 to 2.05), respec-

tively (Table 1). We observed significant positive linear trends in death rates with increasing body-mass index for all cancers, esophageal cancer, stomach cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, prostate cancer, kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and leukemia (Table 1). As compared with men of normal weight, men with a body-mass index of at least 35.0 had significantly elevated relative risks of death from cancer, which ranged from 1.23 (95 percent confidence interval, 1.11 to 1.36) for death from any cancer to 4.52 (95 percent confidence interval, 2.94 to 6.94) for death from liver cancer (Table 1). In the total population of men, a significant inverse association was observed between body-mass index and death from lung cancer. We did not find significant associations between body-mass index and death from brain cancer, bladder cancer, melanoma, or "other" cancers. Among men within the normal weight range, those with a body-mass index of 23.0 to 24.9 were not at higher risk for death from cancer than the leanest men (those with a body-mass index of 18.5 to 22.9), and the observed associations in men were not larger when a leaner group of men was used as the reference group (data not shown).

The results for the total population of women were similar. Women with a body-mass index of at least 40.0 had a relative risk of death from any cancer of 1.62 (95 percent confidence interval, 1.40 to 1.87), as compared with women of normal weight (Table 2). Significant positive linear trends in death rates were observed for colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer, breast cancer, cancer of the corpus and uterus, not otherwise specified, cervical cancer, ovarian cancer, kidney cancer, non-Hodgkin's lymphoma, multiple myeloma, and "other" cancers (Table 2). The highest relative risk we observed was for death from uterine cancer (relative risk, 6.25 for women with body-mass index of at least 40.0; 95 percent confidence interval, 3.75 to 10.42). As in men, a significant inverse association between body-mass index and death from lung cancer was seen in the total population, which included smokers. Significant associations with body-mass index were not observed for death from esophageal cancer, stomach cancer, melanoma, bladder cancer, brain cancer, or leukemia. Although the results for total cancer mortality in women were virtually unchanged when a leaner reference group was used (body-mass index, 18.5 to 22.9), there were significant differences within the

normal weight range for cancers of the gallbladder, breast, and corpus and uterus, resulting in larger elevations in risk for these cancers throughout the entire range of overweight and obesity as compared with the leanest reference group (the relative risk of death from gallbladder cancer for a body-mass index of at least 30.0 was 2.44 [95 percent confidence interval, 1.73 to 3.44]; the relative risks of death from breast and uterine cancers for a body-mass index of at least 40.0 were 2.32 [95 percent confidence interval, 1.54 to 3.50] and 6.87 [95 percent confidence interval, 4.09 to 11.55], respectively).

BODY-MASS INDEX AND MORTALITY FROM CANCER IN MEN AND WOMEN WHO HAD NEVER SMOKED

The association between body-mass index and death from several smoking-related cancers changed when the analysis was restricted to men who had never smoked. The positive associations with death from any cancer, esophageal cancer, pancreatic cancer, and "other" cancers were of greater magnitude among those who had never smoked than in the total population, and the apparent inverse association with death from lung cancer disappeared (Table 3).

As in men, the positive association between body-mass index and death from any cancer, esophageal cancer, and "other" cancers became stronger when the analysis was restricted to women who had never smoked, and the seemingly protective effect of high body-mass index on mortality from lung cancer was attenuated (Table 3). Among women who had never smoked, the relative risk of death from any cancer was 1.88 (95 percent confidence interval, 1.56 to 2.27) for those with a body-mass index of at least 40.0, as compared with women of normal weight.

The relative risks of cancers for which we found significant trends of increasing death rates with increasing body-mass index are summarized for the highest categories of body-mass index that we were able to examine in men (Fig. 1) and women (Fig. 2).

POPULATION ATTRIBUTABLE FRACTION

We estimated the proportion of all deaths from cancer in the U.S. population that are attributable to overweight and obesity to be from 4.2 percent to 14.2 percent among men and from 14.3 percent to 19.8 percent among women (Table 4). The lower estimates are based on relative risks for the entire population, whereas the higher estimates are based

Table 3. Mortality from Cancer According to Body-Mass Index among U.S. Men and Women in the Cancer Prevention Study II Who Had Never Smoked, 1982 through 1998.*

Type of Cancer	Body-Mass Index†					P for Trend
	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0	
Men						
All cancers						
No. of deaths	2119	2638	499	58		
Death rate‡	303.08	346.62	442.00	421.01		
RR (95% CI)§	1.00	1.11 (1.05–1.18)	1.38 (1.24–1.52)	1.31 (1.01–1.70)		<0.001
Esophageal cancer						
No. of deaths	24	52	11			
Death rate‡	3.55	6.82	7.29			
RR (95% CI)§	1.00	1.76 (1.08–2.86)	1.91 (0.92–3.96)			0.04
Pancreatic cancer						
No. of deaths	155	212	34	8		
Death rate‡	22.57	27.87	29.75	60.69		
RR (95% CI)§	1.00	1.24 (1.01–1.54)	1.34 (0.92–1.95)	2.61 (1.27–5.35)		0.005
Lung cancer						
No. of deaths	156	179	30			
Death rate‡	22.72	23.51	23.45			
RR (95% CI)§	1.00	1.00 (0.80–1.24)	0.93 (0.63–1.39)			0.78
All other cancers						
No. of deaths	239	290	81			
Death rate‡	34.65	37.99	62.18			
RR (95% CI)§	1.00	1.06 (0.89–1.26)	1.68 (1.30–2.18)			<0.001
Women						
All cancers						
No. of deaths	6158	3763	1327	288	112	
Death rate¶	241.14	277.92	330.21	356.84	485.06	
RR (95% CI)§	1.00	1.14 (1.09–1.18)	1.33 (1.25–1.41)	1.40 (1.25–1.58)	1.88 (1.56–2.27)	<0.001
Esophageal cancer						
No. of deaths	29	23	14			
Death rate¶	1.08	1.62	2.82			
RR (95% CI)§	1.00	1.49 (0.85–2.59)	2.64 (1.36–5.12)			0.004
Lung cancer						
No. of deaths	476	224	78	17		
Death rate¶	18.71	16.40	19.18	17.51		
RR (95% CI)§	1.00	0.85 (0.73–1.00)	0.99 (0.77–1.26)	0.81 (0.49–1.31)		0.21
All other cancers						
No. of deaths	689	440	146	34	16	
Death rate¶	26.69	31.63	36.24	42.88	72.92	
RR (95% CI)§	1.00	1.17 (1.04–1.32)	1.30 (1.08–1.56)	1.54 (1.08–2.17)	2.51 (1.52–4.14)	<0.001

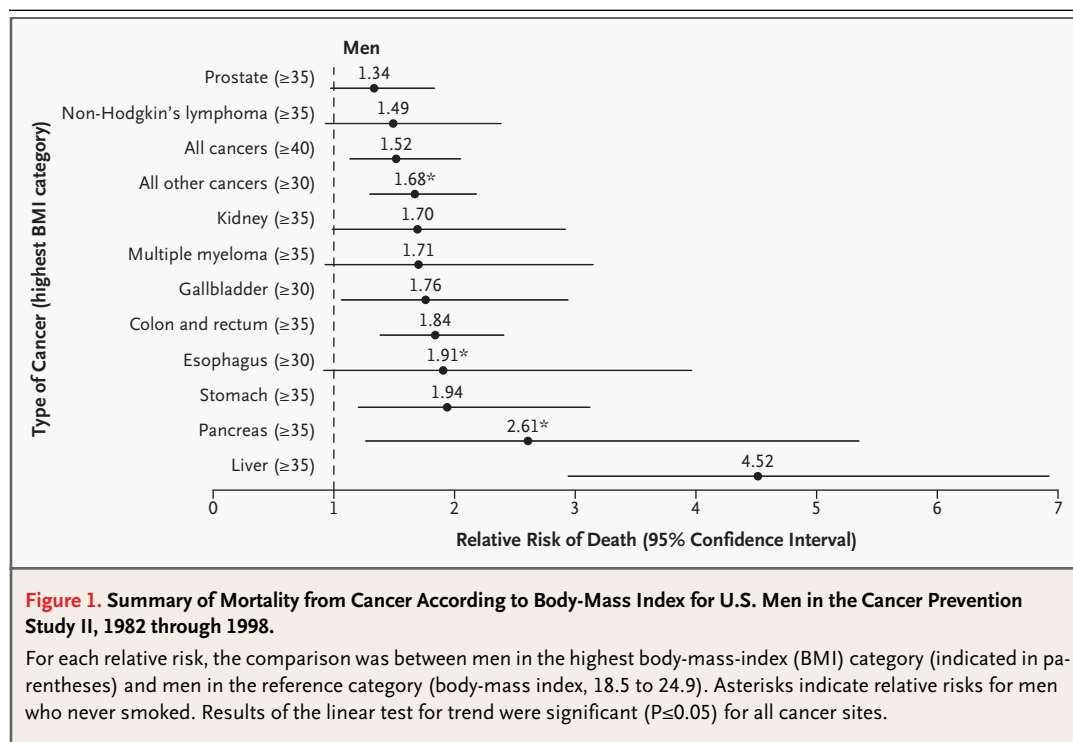
* Participants with any of the following features at study entry were excluded: missing height or current weight; unknown weight one year before entry; weight loss of at least 10 lb (4.5 kg) in the previous year; body-mass index under 18.50; existing cancer (other than nonmelanoma skin cancer); and missing data on smoking status. RR denotes relative risk, and CI confidence interval.

† The highest body-mass-index category examined varies for different cancer sites; upper categories have been combined when necessary because of small numbers.

‡ The rate per 100,000 is given, standardized to the age distribution of men in the Cancer Prevention Study II.

§ The Cox proportional-hazards model was adjusted for age, education, physical activity, alcohol use, marital status, race, aspirin use, estrogen-replacement therapy (in women), fat consumption, and vegetable consumption.

¶ The rate per 100,000 is given, standardized to the age distribution of women in the Cancer Prevention Study II.



on relative risks for those who never smoked. The estimates based on relative risks among men and women who never smoked (Table 4) do not describe the fraction of deaths attributable to overweight and obesity among this population only. Rather, they are estimates of the fraction of deaths attributable to overweight and obesity in the total U.S. population, on the assumption that the relative risks among those who never smoked offer the most valid estimates of the true effect of overweight and obesity on mortality from cancer.

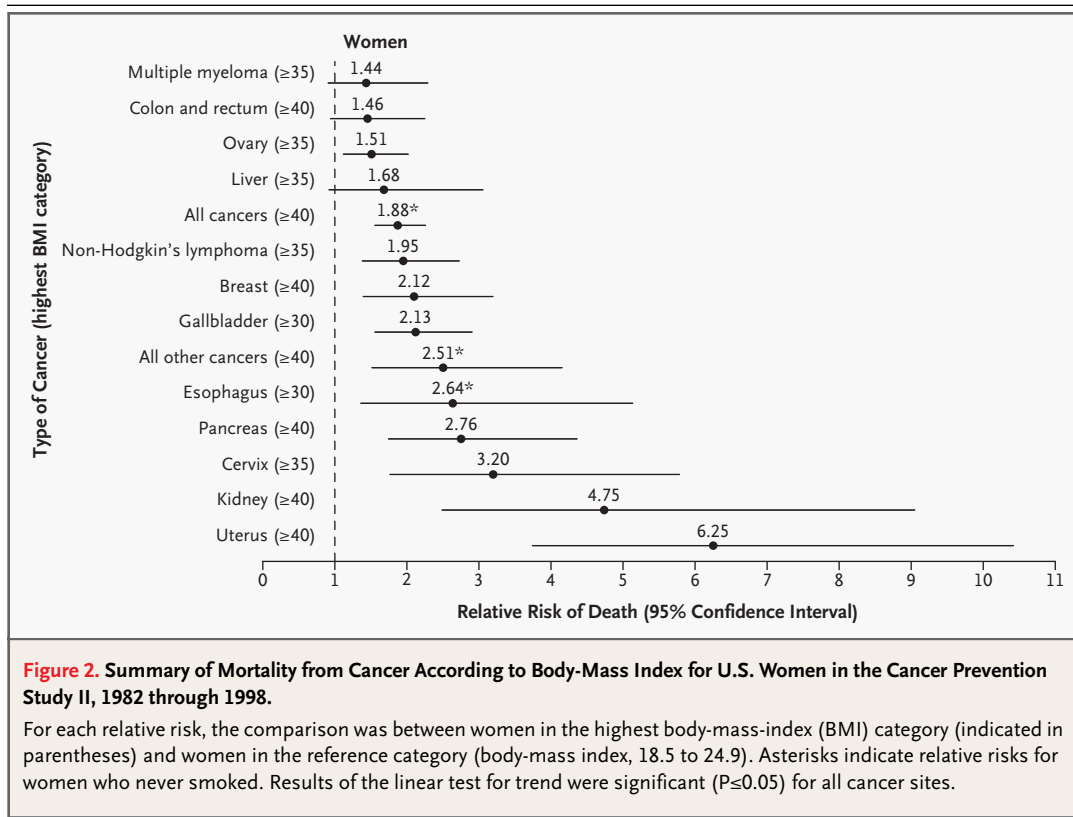
DISCUSSION

The heaviest men and women (those with a body-mass index of at least 40.0) in the large cohort we studied prospectively had death rates from all cancers that were 52 percent and 62 percent higher, respectively, than the rates in men and women of normal weight. This finding is consistent with those of previous studies, but the magnitude of the effect is somewhat larger.^{7,16,17} The stronger associations we found probably reflect our ability to examine deaths from cancer across a wider range of overweight and obesity than has been possible previously. It is also likely that the stronger associations

seen in our study reflect a greater effect of body-mass index on mortality than on incidence of cancer at some sites.^{18,19} These risk estimates are probably conservative, since they are based on the total population, including current and former smokers. Among women who never smoked, the relative risk associated with a body-mass index of at least 40.0 was 88 percent; however, there were not enough deaths among men in this category for us to determine the relative risk.

The proportion of all deaths from cancer that is attributable to overweight and obesity in U.S. adults 50 years of age or older may be as high as 14 percent in men and 20 percent in women. These estimates are based on the relative risks in our study and the current patterns of overweight and obesity in the United States. Under the assumption that these relations are causal, the public health implications for the United States are profound: more than 90,000 deaths per year from cancer might be avoided if everyone in the adult population could maintain a body-mass index under 25.0 throughout life.

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of a cancer-preventive effect of avoidance of weight gain for cancers of the colon, breast (in post-



menopausal women), endometrium, kidney (renal-cell carcinoma), and esophagus (adenocarcinoma).¹¹ Potential biologic mechanisms include increased levels of endogenous hormones (sex steroids, insulin, and insulin-like growth factor I) associated with overweight and obesity and the contribution of abdominal obesity to gastroesophageal reflux and esophageal adenocarcinoma.¹¹ Our study supports the conclusion of the IARC. Moderate relative risks (less than 2.0) associated with overweight and obesity both for colon cancer and for breast cancer in postmenopausal women have been documented consistently in case-control and cohort studies.^{8,34,35} Much higher relative risks have been observed for uterine cancer (2 to 10) and kidney cancer (1.5 to 4), and the increased risk of kidney cancer associated with excess weight is higher in women than in men in this and most previous studies.^{8,36,37} Increases by a factor of two to three in the risk of adenocarcinoma of the esophagus in association with high body-mass index have been reported,^{13,14} and the magnitude of this association has been found by other investigators to be greater in nonsmokers.¹³ Because we could not examine

esophageal cancer according to subsite, the stronger association observed in participants who had never smoked may be partly explained by the greater contribution of adenocarcinoma to all esophageal cancer in nonsmokers than in smokers.¹⁴

Recent studies of gallbladder cancer have consistently found elevated risks for women with a high body-mass index (by a factor of about two) but generally have involved too few cases for the association to be evaluated in men.^{7,16,17,38,39} Obesity may operate indirectly by increasing the risk of gallstones, which, in turn, increase the risk of gallbladder cancer.⁸

Studies suggest that high body-mass index is associated with approximately a doubling of the risk of pancreatic cancer in both men^{15,40,41} and women^{15,41} — a result similar to our findings. In contrast, there is no strong support for an association between body-mass index and prostate cancer.⁴²⁻⁴⁴ However, some data suggest a slight increase in the risk of advanced prostate cancer or death among patients with a high body-mass index.^{19,45,46} Positive associations of ovarian cancer with body-mass index have been found, with relative

Table 4. Estimated Population Attributable Fraction According to Body-Mass Index for Mortality from Cancer in U.S. Men and Women.*

Body-Mass Index	Men			Women		
	Prevalence of Exposure	Relative Risk	Population Attributable Fraction	Prevalence of Exposure	Relative Risk	Population Attributable Fraction
	%		%	%		%
All subjects						
25.0–29.9	42.1	0.97	–1.2	28.8	1.08	2.0
30.0–34.9	21.0	1.09	1.8	22.5	1.23	4.5
35.0–39.9	9.2	1.20	1.8	10.7	1.32	3.0
≥40.0	3.6	1.52	1.9	7.9	1.62	4.9
Total population attributable fraction			4.2			14.3
Subjects who never smoked						
25.0–29.9	42.1	1.11	4.0	28.8	1.14	3.3
30.0–34.9	21.0	1.38	6.8	22.5	1.33	6.1
35.0–39.9†	12.8	1.31	3.4	10.7	1.40	3.5
≥40.0				7.9	1.88	7.0
Total population attributable fraction			14.2			19.8

* Data on prevalence of exposure among men are from the National Health and Nutrition Examination Survey (NHANES) (1999–2000) for U.S. men 50 to 69 years of age. Data on prevalence of exposure among women are from NHANES (1999–2000) for U.S. women 50 to 69 years of age. Data on relative risk are from the Cancer Prevention Study II (Table 1 for data for all men, Table 2 for data for all women, and Table 3 for data for men and women who never smoked). The population attributable fraction was calculated with the use of equation 9.6 in Kleinbaum et al.³²

† Values for men are applicable to men with a body-mass index of 35.0 or higher.

risks in the range of 1.5 to 2.0 for the highest body-mass-index categories studied^{7,47–49}; however, several studies have not shown an association.^{16,17,50,51}

Two studies that examined obesity and liver cancer found an excess risk in both men and women, with relative risks in the range of 2.0 to 4.0^{16,17} — a result similar to our findings. Our results and those of a prospective study in Sweden¹⁶ suggest that this excess risk is higher among men than among women. Obesity also increases the risk of adenocarcinoma of the gastric cardia,^{13,14,52} but the data are limited and inconsistent for noncardia cancers of the stomach.^{13,52} In an earlier American Cancer Society cohort, as in our study, mortality from stomach cancer was associated with body-mass index among men but not among women.⁷ This difference may reflect the greater contribution of the cardia to all cases of gastric cancer in men than in women. Our results for cervical cancer are also similar to those in the earlier American Cancer Society cohort,⁷ where-

as the increased risks observed in two cohorts of hospitalized patients with a diagnosis of obesity, as compared with the general population, were much smaller than those observed in our study.^{16,17} Data are scarce on the relation between hematopoietic cancers and body-mass index, and the findings have not been consistent.^{7,16,17,53}

Our results are based on data on mortality and reflect the combined influence of body-mass index both on the incidence of cancer and on survival, whereas most of the available literature on site-specific cancers is based on incidence data. Our results may be influenced by adiposity-related differences in the diagnosis or treatment of cancer, as well as by true biologic effects of adiposity on survival. For example, adiposity has been shown to be adversely associated with the incidence of breast cancer, survival among women with the disease,⁵⁴ and stage at diagnosis.^{55,56} These combined effects may explain why the association of body-mass index with mor-

tality from breast cancer in our study cohort is somewhat stronger than those in previous studies of incident breast cancer.¹⁸

Smoking profoundly alters the relation between body-mass index and many causes of death. We believe that public health recommendations regarding optimal body mass are most valid when they are based on data from studies of persons who have never smoked.^{5,57,58} For smoking-related cancers, the prospective effects of body-mass index on the risk of death among smokers cannot be separated from the prospective effects of smoking — namely, decreased body mass and increased risk of death. Previous analyses of the Cancer Prevention Study II cohort demonstrated that the apparent inverse association of body-mass index and mortality due to lung cancer was incrementally attenuated with increasingly complex statistical control for smoking in multivariate models, and it disappeared entirely when the analysis was restricted to those who had never smoked.⁵⁹ Thus, for smoking-related cancers, we believe that the estimates of relative risk and population attributable fraction presented for the total population (Tables 1, 2, and 4) are likely to be underestimates, whereas those presented for the population of those who never smoked (Tables 3 and 4) offer the most valid estimates of the true effect of overweight and obesity on mortality from these cancers.

We used self-reported weight and height at study entry to calculate the body-mass index, a widely used index of weight adjusted for height.^{60,61} Although

self-reported weight and height are highly correlated with measured weight and height,⁶²⁻⁶⁴ the small error that exists is generally systematic, with an overestimation of height and an underestimation of weight, especially at higher weights.⁶²⁻⁶⁴ Thus, our measure of body-mass index probably underestimated the true body-mass-index values among overweight persons. We had no direct measure of adiposity or of lean body mass and no measure of central adiposity, such as the waist-to-hip ratio. We also could not evaluate the effect of weight change or weight cycling throughout the follow-up period, and we could not estimate the extent of misclassification that weight change might introduce. The associations observed in this study were not changed in models that excluded deaths in the first two years of follow-up.

The large size of our cohort allowed us to investigate the effect of overweight and obesity on the occurrence of 57,000 deaths from cancer among 900,000 men and women who were free of cancer at base line. Overweight and obesity are associated with the risk of death from all cancers and with death from cancers at many specific sites. From our results, we estimate that 90,000 deaths due to cancer could be prevented each year in the United States if men and women could maintain normal weight. It is unlikely that this goal can be achieved without concerted effort and substantial investment on the part of policymakers, educators, clinicians, employers, and schools to promote physical activity and healthful dietary practices as a cultural norm.

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