

Review

Caloric Intake, Body Weight, and Cancer: A Review

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Abstract

The literature is reviewed for evidence concerning the relation between caloric intake, body weight, and cancer. Convincing experimental data regarding caloric intake and benign and malignant tumor incidence have been available since the 1940s and demonstrate that caloric restriction significantly reduces tumor incidence for a variety of tumor types in several animal models. Some epidemiological investigations provide evidence for a positive calorie-cancer association in humans, although it is difficult (in these studies) to separate the effects of calories per se from those of dietary fat. A larger number of investigations have evaluated body weight alone, and high relative body weight or high caloric intake has been associated with increased risk of cancer of the breast, colon, rectum, prostate, endometrium, kidney, cervix, ovary, thyroid, and gallbladder.

In contrast, lung, bladder, and stomach cancers appear to be inversely associated with body weight, and some prospective studies of men demonstrate greater total cancer mortality among lean individuals. However, in their analyses, few of these latter investigations considered the effects of cigarette smoking, antecedent illness, or competing causes of death. While the relations between caloric intake, other dietary macronutrients (e.g., fat), and body weight are complex and require further investigation, a complete review of the data suggests that reducing caloric intake and relative body weight may lead to a considerable decrease in cancer risk in humans. (Nutr Cancer 9, 199-217, 1987)

Introduction

The deleterious effects of overnutrition and overweight among western populations have been suspected for over a century (1). Since that time, human and laboratory studies have been conducted that provide additional evidence supporting several cancer-diet hypotheses, among them the potential etiologic role of excess caloric intake (i.e., overnutrition). However, compared with other dietary factors such as vitamin A or dietary fat, total caloric intake has received much less attention (2). In addition, the close association between calories and other dietary macronutrients, such as fat and protein, has complicated interpretation of most studies of these nutrients.

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The relation between cancer and body weight in humans has been more widely investigated, demonstrating increased cancer risk among overweight individuals. However, these findings have received cautious interpretation because in some studies cancer mortality was also increased among lean individuals. At the same time, uncertainty exists concerning the exact role of caloric intake in the development of obesity in humans (3). Unfortunately, little effort has been made to resolve these issues and clarify the underlying relationships.

In its 1982 summary statement concerning total caloric intake and cancer, the Committee on Diet, Nutrition and Cancer of the National Research Council concluded that a clear interpretation of the effect of caloric intake on cancer risk could not be made (2). The purpose of this article is to review and critically assess all of the available laboratory and epidemiological evidence for the role of total caloric intake and body weight in the development of cancer.

Animal Studies

A large body of research bearing on the role of caloric intake, body weight, and carcinogenesis is available through the efforts of several laboratories active during the 1940s and 1950s. Tannenbaum and co-workers conducted a long, complementary series of animal experiments investigating various effects of diet on murine tumorigenesis, particularly the role of caloric intake (4-15; for review, see Ref. 16). Their findings are similar to those of other laboratories investigating this area at the time (17-26) and have been more recently corroborated by numerous laboratories (27-41). Briefly, these investigators demonstrated that tumor incidence in rodents is proportional to daily caloric intake; in particular, to intake relative to caloric needs, as evidenced by body weight. Fewer tumors, delayed tumor onset, retarded tumor growth, and fewer metastases were also observed among calorie-restricted animals compared with control animals which were fed more calories ad libitum. In various species and strains, these effects have been demonstrated for a variety of both "spontaneous" and chemically induced neoplasms (including carcinomas, sarcomas, adenomas, and papillomas) of the skin, mammary gland, lung, liver, subcutaneous tissue, blood (e.g., leukemias), and other sites. Because the calorie-restricted animals in these experiments generally lived longer and were often reported as being as active and healthy as their ad libitum-fed controls, the benefit of reduced tumor incidence was not attained by substituting other pathology or by decreasing the animals' life spans.

Of the 45 individual experiments within several studies reviewed by this author that provided adequate information regarding diet, body weight, and tumor incidence, each experiment evidenced a reduction in tumor incidence among the calorie-restricted animals (mice) compared with control animals fed ad libitum (4-6,8-10,32,33). Because conditions other than the diet were reported to be identical for control and experimental groups within each study, pair-wise comparisons within each experiment (and their summary across studies) can be made. The average decrease in lifetime cumulative tumor incidence due to caloric restriction across these experiments was 61%. The average level of caloric reduction achieved among the restricted animals was 32% of the control (i.e., ad libitum) diet (range 7-58%). That is, restricted animals on average consumed approximately two-thirds of the calories fed the control groups. (It is of note that 11 of the 45 experiments demonstrated effective tumor inhibition through only modest caloric reduction; i.e., 7-20%.) Body weight was, in general, directly proportional to caloric intake. Compared with the animals fed ad libitum, the restricted groups weighed less throughout the experiment and on average 27% less (range 5-58%) at the end of the experiments. The statistical significance of the association between caloric restriction and tumor inhibition in these experiments was tested (using chi-square distribution): 21 (47%) of the 45 experiments were significant at $p < 0.001$, 11 (24%) at $0.001 \leq p \leq 0.01$, 4 (9%) at $0.01 \leq p \leq 0.05$, and only 9 (20%) did not achieve statistical significance even though a positive association was demonstrated.

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Results from one series of experiments (10) are demonstrated in Table 1 for "spontaneous" mammary and chemically induced (i.e., 3-methylcholanthrene) skin tumors. Increasing caloric intake and body weight resulted in a greater proportion of animals developing one or more tumors (including skin carcinomas) under otherwise identical experimental conditions, including the age, sex, and strain of the mice, carcinogen dosage (for the induced skin tumors), and the proportion of dietary components (e.g., fat and protein). Minimum incidence was obtained at approximately 60% and 73% of the ad libitum intake levels in the skin and mammary experiments, respectively. The experimental findings and statistically significant test for trend, as well as the results of other experiments, suggest a dose-response relation.

An important issue to be raised is whether the effect demonstrated for caloric intake in these experiments is independent of that due to other individual dietary constituents; for example, dietary fat. In the above experiments, a wide range of fat intake (both absolute and relative to the control animals) was exhibited among the calorie-restricted groups, each of which demonstrated lower tumor incidence compared with controls. These studies demonstrated efficacy of caloric restriction when absolute fat intake (or fat as percent of calories) is kept constant or when adjustment is made for fat intake through multiple regression modeling (D. Albanes, unpublished observations). In addition, in 12 experiments (5,8-10,12,18) caloric restriction (and tumor reduction) was accompanied by somewhat *increased* fat intake.

Many of the above experiments also provided evidence for the tumor-promoting action of dietary fat (6,7,10,18,24,41). A few of these specifically assessed the individual caloric and fat effects and found them to act independently of each other (18,24,41). For example, in one of these studies (18), skin tumor incidence among the four experimental groups was 66, 54, 28, and 0% in the high calorie-high fat, high calorie-low fat, low calorie-high fat, and low calorie-low fat groups, respectively, with both high-low calorie comparisons being statistically significant. Thus, although a tumor inhibitory effect is seen for dietary fat reduction in this and the more recent studies (24,41), the effect of calorie restriction is independent and apparently greater.

Regarding confounding due to differences in micronutrient intake, the earlier "under-feeding" studies involved feeding smaller quantities of the same dietary mixture and therefore resulted in *reduced* intake of vitamins and minerals as well as calories among the animals limited in their caloric intakes (4). These experiments demonstrate efficacy of caloric restriction in reducing tumors despite the diminished intake of several micronutrients suspected today of inhibiting carcinogenesis. Because in most subsequent experiments each comparison study group was fed equal amounts of essential nutrients (e.g., vitamin A), these factors would not have confounded the evaluation of caloric restriction.

There are several additional observations of significance to the potential applicability of these findings to humans. First, animals exposed to either thyroid hormone or low environmental temperatures evidenced fewer tumors than did the control (ad libitum) animals, despite increased caloric intake and decreased body weight (42,43). In addition, efficiency of body weight gain throughout life is associated with increased tumor incidence (35). These data suggest that caloric intake in excess of energy requirements, as evidenced by increased body weight and fatness and not merely the absolute level of intake, is of importance to the tumor-enhancing effects observed.

Second, several experiments demonstrate that intermittent caloric restriction limited to only one day out of every three or four, with ad libitum feeding during the other days, does not decrease tumor incidence, and that more consistent restriction (i.e., daily or every other day) is necessary for efficacy (15,23).

Third, although severe calorie restriction produced the most dramatic results in these experiments, it was not required to decrease tumor incidence; rather, varying degrees of restriction (7-58%) demonstrated efficacy. One-quarter of the experiments involved caloric reduction of $\leq 20\%$ (average 16%) and resulted in an average tumor incidence reduction of 40%.

Table 1. Caloric Intake, Body Weight, and Skin and Mammary Tumor Incidence in Mice^{a,b}

Tumor Type/Sex	No. of Mice	Caloric Intake			Body Weight			Tumor Incidence	
		kcal/day	% of maximum	grams	% of maximum	% (SE)			
Skin tumors (males)	46	8.5	59%	20	59%	15 (5)			
	50	10.0	70%	25	74%	34 (7)			
	50	11.7	82%	27	79%	59 (7)			
	50	14.3	100%	34	100%	86 (5)			
		($p \leq 0.001$)				($p \leq 0.001$)			
Mammary tumors (females)	29	7.8	67%	18	64%	0			
	30	8.5	73%	20	71%	0			
	30	9.4	80%	22	79%	7 (4)			
	30	10.0	85%	23	82%	27 (6)			
		($p \leq 0.001$)				($p \leq 0.001$)			

^a: All *P* values are based on chi-square test for homogeneity.

^b: Data from Tannenbaum (10).

Fourth, some experiments demonstrate efficacy of caloric restriction during the late stages of carcinogenesis (8,36,41). Using a single-chemical tumor induction model, it has been shown that caloric restriction following exposure to the carcinogen is more effective in reducing incidence than restriction prior to or during such exposure (8). Tumor inhibition is also seen among mice fed ad libitum up to approximately "middle-age" (i.e., approx 1 year of age) but restricted thereafter (4,36). Thus, although reduced caloric intake throughout life is most effective in preventing tumors, there is evidence for efficacy even when restriction is instituted at older ages and after carcinogenic exposures.

Human Studies

Evidence also exists for an association between caloric intake, body weight, and cancer in humans. However, there are relatively few epidemiological studies in which caloric intake was directly measured or estimated from either individual or population (i.e., per capita) dietary information and related to cancer risk, and this factor remains unstudied in a large number of diet and cancer investigations. Although assessment of individual dietary intake offers the most direct and valid measure of caloric intake per se, these data are not only difficult to collect but are also not always available through the study method employed (e.g., food frequency questionnaires). In addition, the separation of the effects of total calories from other dietary constituents (notably fat) is not easily achieved (44). Furthermore, few dietary studies evaluate even major sources of caloric expenditure (e.g., basal or resting metabolism or physical activity) to assess caloric intake relative to requirements. Therefore, in human studies where genetics, physical activity, caloric intake, and other factors are less regulated than in the laboratory, indirect markers of relative caloric intake may be more appropriate and meaningful.

The association between cancer and surrogate measures of caloric intake, such as relative body weight (RBW) and body mass indices (BMIs), has been more vigorously investigated. Because caloric intake exceeding the body's energy expenditures is stored primarily as adipose tissue, both increased relative body weight and body mass indices (e.g., weight/height²), which effectively adjust weight for stature and therefore give a better assessment of excess weight or fatness per se, will in general reflect individual positive energy balance (45,46). Conversely, caloric restriction results in lower RBW and BMIs. Although for a small proportion of individuals increased lean body mass (and not adipose tissue) may account for increased RBW or BMI, in the general population, these anthropometric parameters are highly correlated with other measures of fatness (e.g., skinfold thickness) and are therefore useful indicators of excess body fat (47). These surrogate measures of caloric intake are therefore relevant to the discussion of caloric intake and cancer.

Alternatively, body weight represents a composite measure of lean body mass and height or frame size, in addition to fatness or obesity. Consequently, even though increased caloric and protein intake during development promotes greater growth and stature and increased lean body mass can result from (as well as necessitate) increased caloric intake in adults, taken by itself, body weight remains a less-sensitive indicator of relative caloric intake than do RBW or BMIs. Body weight does, however, offer an estimate of the effect on cancer risk of overall adult size and the cumulative caloric exposure that it represents (at the same time acknowledging the existence of other determinants of body size such as heredity).

Caloric Intake and Cancer

Investigations of the relation between caloric intake and cancer include two cross-sectional and two case-control studies. The first of these, an international correlation study by Armstrong and Doll (48), demonstrated that countries exhibiting increased availability of total food calories experienced greater cancer incidence and mortality than did lower-calorie na-

tions. Site- and sex-specific correlation coefficients (r) based on concurrent per capita food data and cancer rates for 1955–1967 in 37 countries were presented in their report; this report evidenced significant associations between total calories and cancer of the breast, colon, rectum, uterus, and kidney in women (r values of 0.57, 0.66, 0.56, 0.65, and 0.64, respectively) and cancer of the colon, rectum, kidney, and nervous system in men (r values of 0.60, 0.75, 0.55, and 0.56, respectively). The level of total calories was highly correlated with several other dietary and environmental factors in these data (including total fat or animal protein in the diet), some of which exhibited somewhat higher correlation coefficients for some cancer sites. For example, compared with the correlations between colon cancer incidence and calories of 0.60 and 0.66 for men and women, respectively, the r values for total fat were 0.74 and 0.78. No discriminating assessment of the independent effects of these factors was presented, however.

In the cross-sectional study of colorectal cancer mortality in Hong Kong by Hill and co-workers (49), a greater than twofold rate increase was observed for persons in the highest of three family income categories compared with the lowest income group (in males, 26.7 vs. 11.7/100,000). This was related to an increased consumption of all foods by high-income individuals, including estimated daily caloric intake (i.e., 3,900 vs. 2,700 kcal in the low-income population).

Although a large number of case-control studies of diet and cancer have not evaluated total caloric intake, two such case-control studies assessing the role of dietary intake in cancer demonstrated a positive association between total caloric intake and cancer risk. In the study by Miller and colleagues (50), which reported an association between dietary fat and breast cancer, mean daily caloric intake of breast cancer cases was also slightly, but significantly, higher than that of controls. This association was stronger among postmenopausal women (2,170 vs. 2,115 kcal daily) than among premenopausal women (2,373 vs. 2,339 kcal). However, no dose-response relation was evidenced for caloric intake, with risk ratios of 1.3 and 1.1 for premenopausal women of moderate or high (>2,500 kcal) daily intake compared with the $\leq 2,000$ kcal group, respectively. Among postmenopausal women, risk ratios of 1.0, 0.8, and 1.2 were obtained for three increasing quartiles compared with the group ingesting less than 1,500 calories daily; in comparison, risk ratios were higher for the three increasing quartiles of total fat (1.7, 1.2, and 1.8) and saturated fat (1.2, 1.1, and 1.2).

In contrast to this study, Jain and others (51) observed a significant, positive dose-risk association for total calories among both men and women in their study of cancer of the colon and rectum. Relative risks of 1.5 and 1.8 were demonstrated among men for the medium (2,485–3,255 kcal/day)- and high (>3,255 kcal/day)- intake groups compared with the low-intake group (<2,485 kcal/day). The corresponding risk ratios among the women were 1.6 and 2.2, using 1,760 and 2,360 kcal as tertile boundaries. While risk ratios for total fat intake were equivalent to those for calories in this study, somewhat higher values (2.4 and 2.6 for the high tertiles in men and women, respectively) were exhibited for saturated fat.

Thus, in both case-control studies and the international correlation investigation discussed above, dietary fat exhibited similar or somewhat stronger associations with cancer. However, the independent effects of total calories and fat were not separated because of the high degree of correlation between these factors.

Body Weight, Body Mass Indices, and Cancer

Twenty-four retrospective studies of the relationship between body weight, relative body weight, BMIs, and cancer from several countries are summarized in Table 2. Each investigation demonstrated a positive association between increased body weight or fatness and cancer risk, with the exception of two studies of breast cancer (56,57), one study of prostate (72), and one study of colorectal cancer (73). Of all the investigations, 8 assessed only absolute body

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Table 2. Retrospective Human Studies Relating Body Weight and Cancer

First Author/ Reference No./Year	Location	No. of Cases	Factor(s) Studied	Findings	Comments
Breast de Waard (52) 1964	The Netherlands	300	RBW ^a	Postmenopausal cases more overweight than controls; RR ^b = 1.3 and 1.6 for obesity and obesity plus hypertension; opposite trend in premenopausal women	No statistical tests presented
Valaoras (53) 1969	Greece	758	BW ^c BMI ^d	RR = 1.0, 1.5, 1.9, 1.7, 1.9, 1.7, 1.7, and 1.8 for BW categories <55 to ≥85 kg; <i>p</i> ≤ 0.01 ^e RR = 1.0, 1.3, 1.6, 1.2, 1.3, and 1.7 for BMI categories <22.0 to ≥30.0; <i>p</i> ≤ 0.02	Positive association with height
Mirra (54) 1971	Brazil	536	BW BMI	RR = 1.0, 1.6, 2.3, and 2.5 for BW categories <55 to ≥75 kg; <i>p</i> < 0.001 RR = 1.0, 0.9, 1.5, and 1.6 for BMI categories <22.0 to ≥27.0; <i>p</i> < 0.01	Associations observed among women ≥50 years old only; positive association with height
Lin (55) 1971	Taiwan	213	BW	RR = 1.0, 1.6, 1.5, 2.5, and 2.0 for categories <45 to ≥60 kg; <i>p</i> < 0.01	Increased effect among women ≥50 years old; no effect for height
Adami (56) 1977	Sweden	179	BW BMI	No significant case-control differences in mean BW (66.3 vs. 66.0 kg) or BMI (25.5 vs. 25.4) among postmenopausal women	Opposite trend in premenopausal women also not significant; no effect for height; used measured BW for cases, self- reported BW for controls
Soimi (57) 1977	Finland	122	BW BMI	No significant case-control differences for either BW or BMI	Nonsignificant positive association with height; limited age range (41-60 years), and no analysis by menopausal status
Hirayama (58) 1978	Japan	400	BW	RR = 1.0, 4.8, 4.5, and 12.4 (postmenopausal) and 1.0, 1.3, 2.1, and 3.0 (premenopausal) for 4 obesity categories: thin, ordinary, slightly obese, obese; <i>p</i> < 0.01	Independent positive associations for both BW and height

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Table 2. Continued

First Author/ Reference No./Year	Location	No. of Cases	Factor(s) Studied	Findings	Comments
<i>Breast</i> Choi (59) 1978	Canada	400	BW	Increased mean BW for postmenopausal cases, especially for older women and BW at time of menopause (71.7 vs. 60.6 kg for age ≥ 70 years; $p = 0.03$); decreased BW for premenopausal cases (59.6 vs. 63.5 kg; $p = 0.01$)	Postmenopausal cases also taller
Paffenbarger (60) 1980	US	1,403	BMI	RR = 1.0, 1.3, and 1.4 (postmenopausal; $p \leq 0.05$) and 1.0, 0.9, and 0.7 (premenopausal; $p \leq 0.01$) for categories < 21.5 to ≥ 24.5	Similar trends for BMI at age 20 and BW gain since age 20; increased height in premenopausal cases
Kelsey (61) 1981	US	332	BW	RR = 1.6 for postmenopausal women > 56.8 kg, $p = 0.05$; RR = 0.4 for premenopausal women > 75 vs. ≤ 56.8 kg, $p = 0.02$	
Brisson (62) 1984	US	362	BW	RR = 1.0, 1.3, 2.3, and 2.7 for categories < 55 to ≥ 75 kg; $p \leq 0.05$	Effect in pre- and postmenopausal women; inverse association with height
<i>Kidney</i> Wynder (63) 1974	US	202	RBW	Greater proportion of cases (29 vs. 10%) with RBW $\geq 125\%$ among women only ($p \leq 0.05$) and more underweight persons among controls	
McLaughlin (64) 1984	US	495	BMI	RR = 1.0, 1.2, 1.7, and 2.3 for categories ≤ 21.6 to > 26.2 in females; ($p < 0.01$); RR = 1.0, 0.9, 0.8, and 1.3 for categories ≤ 23.6 to > 27.9 in males; NS	Positive association observed for weight gain since age 20 and in older ages (females)
Maclure (65) 1985 (abstr)	US	355	BMI	RR = 3.0 for high vs. low quintile in women; RR = 2.0 in men	
Goodman (66) 1986	US	267	BMI	RR = 2.7 for categories > 28.0 vs. < 24.0 for men ($p < 0.01$); RR = 2.4 in women ($p < 0.05$)	
Asal (67) 1985 (abstr)	US	315	BMI	RR = 2.2 for high vs. low quintile of BMI at age 20 in men; RR = 2.7 in women; RR = 3.0 for men if current BMI used	

Yu (68) 1986	US	267	BMI	RR = 2.7 for categories > 28.0 vs. < 24.0 for men ($p < 0.01$); RR = 2.4 in women ($p < 0.05$)	in men	Similar trends with higher RR for BMI 10 years prior to study and at age 20; independent of tobacco and other risk factors
Goodman (66) 1986	US	315	BMI	RR = 2.2 for high vs. low quintile of BMI at age 20 in men; RR = 2.7 in women; RR = 3.0 for men if current BMI used		
Asal (67) 1985 (abstr)	US	160	BMI	RR = 1.0, 1.2, 1.6, and 1.8 for quartiles of BMI among males; RR = 1.0, 0.8, 2.0, and 2.7 for women ($p < 0.05$ for linear trend)		
<i>Endometrium</i> Kelsey (69) 1982	US	167	BW	RR = 1.0, 1.3, 1.3, and 2.3 for categories ≤ 56.9 to > 75.0 kg; $p = 0.001$		Similar trend for BMI (not presented by authors)
Henderson (70) 1983	US	127	BW	RR = 1.0, 1.5, 2.0, 9.6, and 17.7 for categories < 59.0 to > 86.1 kg; $p < 0.001$		Similar trends for BMI and BW at age 20
La Vecchia (71) 1984	Italy	283	BMI	RR = 1.0, 1.6, 3.3, and 7.6 for categories < 20.0 to > 30.0 in postmenopausal women ($p < 0.001$); RR = 1.0, 1.5, 3.9, and 20.3 for same categories in premenopausal women ($p < 0.001$)		
<i>Prostate</i> Wynder (72) 1971	US	300	RBW	No significant difference in RBW between cases and controls		No significant difference in height
<i>Colorectal</i> Wynder (73) 1969	Japan	107	RBW	No significant difference in RBW between cases and controls		
<i>Thyroid</i> McTiernan (74) 1985 (abstr)	US	182	BW	RR = 3.0 for category ≥ 60.0 vs. ≤ 52.0 kg in women		Study of females only
<i>Meningioma</i> Bellur (75) 1983	US	176	RBW	RR = 4.2 for "obese" women; $p < 0.001$		No significant difference among men

a: RBW, relative body weight.
 b: RR, relative risk.
 c: BW, body weight.
 d: BMI, body mass index.
 e: P values for test for trend, unless otherwise indicated.

weight, whereas 16 involved relative weight or a BMI. (Unless otherwise specified, in Tables 2 and 3 BMI refers to the index weight/height², which is also known as the Quetelet index.) Although the weight or BMI categories and their associated risk estimates varied somewhat between studies, relative risks of two or more were typically evidenced for the highest compared with the lowest weight or obesity index quantile. In most reports a dose-response relation was demonstrated. Some studies also evidenced a positive association with cancer for weight gain in adulthood or for height, whereas others showed an inverse association between weight or BMI and cancer among premenopausal women. It is of note that in only eight of the reports (52,53,56,59,61,62,68,75) were the methods of body size assessment explicitly stated (e.g., self-reported vs. measurement), although for many the use of self-reported information was suggested.

Prospective studies that have investigated the relation between body weight or obesity and cancer incidence or mortality are presented in Table 3. Of the four studies of cancer incidence, two involved total cancer or multiple sites (80,89) and two investigated breast cancer only (85,86). Of the 11 mortality studies, 7 assessed total cancer mortality only (76-79,81-83), 1 assessed site-specific and total cancer mortality (90), and 3 assessed site-specific mortality only (84,87,88). Only six of the investigations reported findings in women (77,78,80,85,86,90). Overall, the studies support an association between obesity and cancer but also point to increased cancer of some sites among the most underweight individuals, primarily in men.

Analyses of life insurance company records, such as the study of Dublin (76), represent some of the earliest evidence concerning the association between body weight and cancer mortality in humans. In this study, the mortality experience of approximately 192,000 men was assessed and demonstrated a clear trend for increasing cancer mortality rates among men with greater relative weight, the lowest rate being observed among men 15-50% underweight. However, these data reflect mortality rates unadjusted for differences in age between weight categories. [Tannenbaum (91) reviewed six of these early studies, all but one of which were supportive of the hypothesis that relative body weight is positively related to cancer mortality.] In both the Build and Blood Pressure Study (BBPS) (77) and its successor, the Build Study (BS) (78), higher cancer mortality ratios were observed for the most overweight women. In addition, the latter study demonstrated increased mortality among men and women more than 14% underweight. The mortality ratios reported, however, represent the actual (or observed) cancer mortality compared with the total all cause mortality rate of the cohort by sex and weight groups. Because overweight (and not underweight) individuals in these studies experienced greatly increased mortality due to several other illnesses (including cardiovascular, renal, and gastrointestinal diseases as well as diabetes mellitus), the comparison of cancer mortality to total mortality in this manner would necessarily reduce the observable excess cancer deaths in the overweight categories.

Seven reported investigations of the relation between cancer incidence or mortality and body weight or mass have been conducted in the context of prospective cardiovascular studies (79-84,89). Comparing the Framingham study data to the BBPS data discussed above, Sorlie and colleagues (79) demonstrated somewhat increased total cancer mortality among men in the lowest relative body weight category during the initial six years of follow-up. Wallace and co-workers (80) evidenced reduced BMI among men and women who later developed cancer (compared with noncancer controls). However, the association was significant only among a) those ≤ 59 years old at the time of study entry, b) for "smoking-related" cancers, and c) for malignancies occurring more than two years after study entry. Using data available from the Whitehall Study, Jarrett and others (81) showed that increased total cancer mortality in the lowest BMI quintile and an overall inverse association were due to underweight cases diagnosed primarily within two years of study entry. The BMI-cancer mortality relation beyond two years of follow-up was J-shaped, with increased cancer beginning in the second lowest quintile. Avons and colleagues (82) also demonstrated that men in the lowest quintile of BMI

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Table 3. Prospective Human Studies Relating Body Weight and Cancer

First Author/ Reference No./ Place/Period	Study Population	Factors Studied	Findings							Comments		
<i>Total Cancer</i> Dublin (76) US 1887-1921	Approx. 192,000 males, ages ≥ 45 years	RBW ^a Mortality	RBW % Rate/10 ⁵	50-84 95	85-94 114	95-104 111	105-114 121	115-124 138	≥ 125 143	Crude mortality rates only		
Society of Actuaries (77) US 1935-1953	Approx. 4,900,000 males and females, ages 15-69 years; 133,000 deaths	RBW Mortality ratio (%)	RBW % Ratio Male Female	60-85 116	84-110 100	111-134 100	135-154 110	155-174 116	≥ 175 105	Age-adjusted mortality ratios for both Society studies based on expected death from all causes; BW ^a reduction associated with decrease in total mortality		
Society of Actuaries (78) US 1954-1972	Approx. 4,200,000 males and females, ages 15-69 years; 106,000 deaths	RBW Mortality ratio (%)	RBW % Ratio Male Female	-65-75 130	-85 109	-105 84	-115 85	-125 93	-135 94	-145 93	-155 133	Inverse relation primarily among smok- ers and during the first 12 years of follow-up for total mortality
Sorlie (79) US 1949-1973	5,209 males and fe- males, ages 30-62 years; 1,295 deaths	RBW Mortality		Slight inverse relation between 6-year cancer death rate and RBW in men; data for cancer not shown for women; data presented graphically only								
Wallace (80) US 1973-1980	5,565 males and fe- males, ages 20-94 years; 131 cases	BMI ^c Incidence		No significant case-control differences in BMI except among persons ≤ 59 years old; males 25.8 vs. 27.7, females 24.6 vs. 27.3; <i>p</i> < 0.05 (paired <i>t</i> -test)								
Jarrett (81) UK 1967-1976	18,393 males, ages 40-64 years; 1,722 deaths	BMI Mortality	BMI quintiles Rate (total)/1,000/year Early rate (<2 years) Late rate (2-10 years)	(≤ 22.4)	Q1 3.2	Q2 2.6	Q3 3.0	Q4 3.0	Q5 3.0	(> 27.0)	Excess total mortality among lean indi- viduals observed at older ages (≥ 55 years) only	
Avons (82) France 1967-1977	7,591 males, ages 43-53 years; 908 deaths	BMI Mortality	BMI quintiles Rate/1,000/year Rate for BMI change (Q1-Q5, <0.5 to >6.5)	(< 23.0)	Q1 5.2	Q2 2.3	Q3 1.9	Q4 1.9	Q5 2.4	(> 28.5) (<i>p</i> < 0.001) ^d (<i>p</i> < 0.01)	No trend for BMI at age 20	
Rhoads (83) US 1965-1974	8,006 males, ages 45-68 years; 223 deaths	BMI Mortality	BMI quintiles Rate/1,000/year Rate for BMI at age 25	(< 21.2)	Q1 3.9	Q2 3.2	Q3 2.7	Q4 1.6	Q5 2.2	(> 26.3) (<i>p</i> < 0.001) (<i>p</i> > 0.05)	Excess cancer mortality in lean men (Q1, Q2) restricted to those who lost weight after age 25	
<i>Lung</i> Garn (84) Scotland 1965-1980	2,381 males, ages 45-75 years; 103 deaths	BW BMI Mortality	Fatness level Weight Weight/Height	Low 5% (lean)	Medium 15-85%	High > 85% (obese)	Lung cancer deaths as % of total mortality			Findings for other sites not reported; skinfold thickness also associated		
				6.2%	4.2%	4.1%	3.2%	3.2%	2.9%			

(Continued)

Table 3. *Continued*

First Author/ Reference No./ Place/Period	Study Population	Factors Studied	Findings	Comments
<i>Breast</i> de Waard (85) The Netherlands 1964-1973	7,259 females, ages 55-75 years; 70 cases	BW BMI Incidence	RR = 1.0, 2.1, 2.2, 3.5, and 3.0 for BW <60 to ≥90 kg RR = 1.0, 0.8, 0.9, 1.3, and 1.2 for BMI <25 to ≥31	Independent effects for BW and height; study implicates "largeness" more than obesity per se; no statistics presented
Willert (86) US 1976-1980	121,964 females, ages 30-55 years; 570 cases	BW BMI Incidence	RR = 1.0, 0.9, 1.0, 0.9, and 1.0 (postmenopausal) and RR = 1.0, 0.9, 0.9, 0.7, and 0.7 (premenopausal) for BMI quintiles (categories not provided)	Excess incidence in lean premenopausal women limited to smaller, well- differentiated tumors suggesting diag- nostic bias; BW and height were also minimally related to cancer (inversely and directly, respectively)
<i>Prostate</i> Greenwald (87) US 1880-1967	Approx. 18,000 males, college age; 268 deaths	BW BMI Mortality	No significant case-control differences in BW or BMI (ponderal index: height/BW ^{1/3})	No effect for height or various somatotypes
Snowdon (88) US 1960-1980	6,763 males, ages ≥40 years; 99 deaths	RBW Mortality	RBW (%) 70-89 90-109 110-129 130-245 RR = 1.6 1.0 1.2 2.4 (p ≤ 0.05)	Independent increase in RR for heavy consumers of meat, milk, cheese, and eggs
<i>Multiple Sites</i> Nomura (89) US 1965-1979	8,006 Japanese males, BMI ages 45-68 years; 646 cases	BMI Incidence	BMI quintile Rate/1,000/year Stomach (<21.3) Q1 Q2 Q3 Q4 Q5 (>26.3) Colon 26.4 15.8 10.3 4.2 12.3 (p < 0.001) Prostate 12.2 11.6 15.7 12.9 17.4 (p = 0.17) 11.4 9.8 15.4 13.3 14.2 (p = 0.24)	Stomach and lung cancer account for in- verse association with total; trend for colon cancer restricted to ages ≥55 and is associated with BW gain since age 25
Lew (90) US 1959-1972	755,500 males and fe- males, ages ≥30 years	RBW Mortality	See Table 4	

a: RBW, relative body weight.

b: BW, body weight.

c: BMI, body mass index.

d: P values for test for trend, unless otherwise specified.

a: RBW, relative body weight.

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experienced the highest total cancer mortality rate. While reported BMI at age 20 showed no association with cancer, men with weight loss (i.e., BMI change) after age 20 experienced much higher cancer mortality. These results were very similar to the findings of Rhoads and Kagan (83), who found increased cancer mortality among the leanest men at examination accounted for by those who lost weight since age 25, whereas the leanest at age 25 evidenced the lowest cancer rate.

Five prospective investigations of single cancer sites have been reported. In a study of mortality among men from the West of Scotland, Garn and co-workers (84) using various measures of body fatness (including skinfold thickness and radiographic fat shadows) noted increased lung cancer mortality among the leanest men compared with those most obese, who instead experienced greatly increased cardiovascular disease mortality. Studying the determinants of postmenopausal breast cancer, de Waard and Baanders-van Halewijn (85) showed that body weight (and to a lesser degree, BMI) was positively associated with incidence. In contrast, Willett and co-workers (86) showed little association between postmenopausal breast cancer and BMI, but they did demonstrate a statistically significant inverse association in premenopausal women, which was attributed to easier (and early) diagnosis in lean individuals. Greenwald and others (87) failed to demonstrate a difference in weight, ponderal index, or somatotype between men who developed prostate cancer and those who did not, whereas Snowdon and colleagues (88) evidenced increased prostate cancer mortality among overweight men (relative risk = 2.4 for men $\geq 130\%$ RBW vs. 90-109% RBW group). Similar findings for breast and colon cancers were reported in the latter study, but data for these sites were not presented.

In a follow-up to a previous report examining total cancer mortality (83), Nomura and co-workers (89) demonstrated that BMI at entry was positively associated with the risk of colon and prostate cancers and negatively associated with the risk of stomach and lung cancers. The association for colon cancer was seen among those ≥ 55 years old at the time of examination and those who gained weight after age 25, whereas a stronger positive association for prostate cancer was evident for BMI at age 25. Weight loss since age 25 was associated with stomach and lung cancer incidence and was observed among cancers developing within 5 years (stomach) and 10 years (lung) after examination. These findings contrast with those concerning only total cancer mortality, thus pointing out the possibility of significant site-specific differences being overlooked in analyses of total incidence or mortality.

Between 1959 and 1972, the American Cancer Society conducted a prospective study of 755,500 men and women in the United States (90). In this study, total mortality increased linearly with RBW, with all major causes of death contributing to the observed trend. Some of the findings with respect to cancer risk and weight appear in Table 4. Total cancer mortality was higher among those overweight (i.e., $> 110\%$ of average) when compared with those 90-109% of average weight. For men, this relation was statistically significant for cancer of the colon, rectum, and prostate, whereas in women, cancer of the breast, uterus (cervix and endometrium), gallbladder, and ovary was most increased among those overweight. Persons in the underweight categories in general experienced reduced cancer mortality compared with the average weight group, except for cancer of the lung in both men and women and cancer of the stomach, bladder, and pancreas in men. (Note that these are all cancers associated with cigarette smoking.)

Discussion

The laboratory has offered some advantages over human studies in the investigation of this area. It has been possible to evaluate the effect of a wide range of caloric intakes and resulting body weights simultaneously, and several experiments evidenced dose-response relations between both factors and cancer incidence. Intake of potentially confounding dietary constitu-

Table 4. Cancer Mortality Ratios^a According to Relative Body Weight and Cancer Site^b

Site	Sex	Relative Body Weight						
		< 80%	80-89%	90-109%	110-119%	120-129%	130-139%	≥ 140%
All cancers	M	1.33	1.13	1.00	1.02	1.09	1.14	1.33
	F	0.96	0.92	1.00	1.10	1.19	1.23	1.55
Colorectal	M	0.90	0.86	1.00	1.26	1.23	1.53	1.73
	F	0.93	0.84	1.00	0.96	1.10	1.30	1.22
Breast	F	0.82	0.86	1.00	1.19	1.16	1.22	1.53
Prostate	M	1.02	0.92	1.00	0.90	1.37	1.33	1.29
Endometrium	F	0.89	1.04	1.00	1.36	1.85	2.30	5.42
Gallbladder	F	0.68	0.74	1.00	1.59	1.74	1.80	3.58
Lung	M	1.78	1.38	1.00	0.85	1.04	1.00	1.27
	F	1.49	1.20	1.00	1.10	1.06	1.06	1.22
Bladder	M	1.47	1.27	1.00	0.95	0.95	0.95	

a: Mortality ratio is the age-adjusted and sex-specific mortality rate in a specific weight category divided by the rate for persons in the average body weight category (90-109% of the mean weight for height).
b: Data from Lew and Garfinkel (90).

ents was controlled, and other experimental factors, such as the age or genetic strain of the animals (or the carcinogen dosage, if an induction model), were equivalent between groups within individual experiments. Although shorter periods were also evaluated, lifetime patterns of caloric exposure were usually tested, and several studies demonstrated diminished longevity and increased mortality from all causes among overfed and overweight animals.

Human studies corroborate many of these experimental findings. Cancer incidence and mortality increase with excess body weight (and to a lesser degree caloric intake), and many investigations demonstrate increased morbidity and mortality from several causes among obese individuals. Persons with increased caloric intake or relative body weight are at increased risk of cancer of the breast, colon, rectum, prostate, endometrium, kidney, cervix, ovary, gallbladder, and thyroid, and many studies suggest dose-risk trends. Some studies implicate not only obesity but also large frame (e.g., height) and body size (e.g., weight), findings also consistent with increased caloric intake. Both the diversity of sites affected and the magnitude of rate increases observed are in line with the laboratory findings. In contrast with these observations, however, are several prospective investigations also demonstrating increased rates of total cancer (77-79,81-83,89,90) and, specifically, cancer of the lung (84,89,90), stomach (89,90), and bladder (90) among lean individuals, primarily males. These paradoxical findings, which are in conflict with laboratory studies showing only reduced tumor incidence and overall mortality among calorie-restricted and underweight animals, may be due to several factors, including confounding, antecedent disease, and competing causes of death.

Although some investigators adjusted for potential confounders in their analyses, many did not. Because lung and bladder (and possibly stomach) cancer are associated with cigarette smoking and because individuals who smoke are more likely to be lean than those who do not (92,93), cigarette use may have biased the findings in several of the studies that demonstrated increased cancer mortality among underweight individuals. This is true not only of studies of these individual sites but also of investigations of overall cancer mortality, because lung cancer is usually a major determinant of total cancer rates (89,90). One measure of this confounding is available from the American Cancer Society study, which revealed that the excess cancer among lean individuals was confined to smokers, particularly those who smoke 20 or more cigarettes per day (90). Among nonsmokers, in contrast, a nearly linear trend between RBW and total cancer mortality was observed for both men and women, demonstrating that leanness in the absence of exposure to cigarettes was protective against cancer. The finding in sev-

Cancer Site ^b
% ≥ 140%
1.33
1.55
1.73
1.22
1.53
1.29
5.42
3.58
1.27
1.22

Category divided by (or height).

eral studies that weight loss after age 20 or 25 is associated with increased cancer mortality later in life is also consistent with the effect of lifetime cigarette smoking on both body weight and cancer risk. Furthermore, because smoking-related cancer mortality is greater in men than in women, such a confounding effect could also partly explain the apparent sex difference with regard to leanness and increased cancer mortality.

Another factor that may account for leanness and weight loss among persons later developing cancer is antecedent illness. Screening individuals for major diseases prior to study entry, as was done in some prospective investigations (77,78,89,90), would reduce such a bias. Other investigations evaluated follow-up time. Four studies which assessed the time interval between body size determination at study entry and the development of cancer or death have demonstrated that excess mortality among those underweight occurred during the early follow-up period (usually within 5 years) (77,78,81,89). Only one (smaller) study showed an opposite trend (80). In light of these findings, failure to demonstrate increased leanness among cases in the *retrospective* studies reviewed suggests either site-specific differences of this effect (i.e., lung and gastric greater than breast and renal cancer) or underestimated relative risks in the retrospective studies.

Competing causes of death may also account for the observed excess cancer deaths among the leanest individuals. Because in most of these studies the overweight experienced increased mortality from cardiovascular disease and several other major causes of death, some overweight individuals who could have gone on to develop cancer may have died of other causes, whereas leaner individuals less prone to other illnesses would become overrepresented among the cancer cases. Thus, assessment of cancer mortality from the cardiovascular disease study cohorts may result in biased conclusions concerning body weight. This factor could also account for some of the observed sex difference.

Several mechanisms can be forwarded to explain the observations presented in this report, although few have been adequately evaluated. By limiting body size and weight, a reduced absolute number of cells in various organ systems would be at risk for malignant transformation (94). Reduced mitotic activity has been observed among calorie-restricted animals (95), and basal (or resting) metabolic rate is proportional to caloric intake and relative body weight in both animals and humans (45,96). The probability of creating or propagating heritable malignant changes could be affected by these processes. Changes in intake of carcinogens from food sources, or changes in amount or type of intestinal microflora, bile acid production, or carcinogen production and/or activation in the gut, might also be related to changes in the level of caloric intake and obesity. Alternatively, through effects on the immunologic or endocrine systems, tissue susceptibility to various mechanisms of malignant transformation may be altered (22,41,97,98).

Conclusion

Observations based on animal experiments demonstrate the dependence of benign and malignant tumor incidence on the level of caloric intake and body weight. Epidemiological studies support a positive association between increased caloric intake and body size or fatness and cancer in humans; however, studies concerning caloric intake per se are relatively few and are complicated by other macronutrients such as dietary fat. Conflicting reports regarding body weight may be explained in terms of the effects of confounding factors (e.g., cigarette consumption), antecedent disease, and/or competing causes of death. While some researchers have acknowledged an important role for caloric intake in carcinogenesis, they have at the same time rejected the concept of caloric restriction as extreme and impractical for human intervention (99,100). An apparent dose-response relation suggests, however, that any effort at reducing caloric intake and body weight would diminish the risk of cancer, and while lifetime restriction appears most efficacious, sustained reduction in adulthood may also be beneficial.

Based on available evidence, several areas for further research are recommended. Animal

experiments should be conducted to further separate the tumor-promoting effects of total calories from specific dietary constituents (e.g., fat, both amount and type); studies also need to evaluate potential mechanisms of action for the effects of caloric intake and body weight on tumorigenesis (e.g., through effects on metabolism or the immune or endocrine systems). Human investigations (including laboratory studies) of the relation between total calories and dietary fat (and other dietary factors), physical activity, and anthropometric parameters (including weight and skinfold thicknesses) may also help clarify some of the existing evidence. Finally, epidemiological investigations (preferably prospective, given the known metabolic effects of cancer) that collect data concerning caloric intake and expenditure, anthropometric parameters (if possible, at various periods in life), and potential confounding factors, dietary or otherwise, should be undertaken. Some of the diet-cancer intervention trials currently being conducted, although they do not test caloric intake specifically, may also shed some light on this issue. Given the benign nature and overall health promotional effect of caloric and weight reduction for overweight individuals, human trials of this hypothesis may be warranted.

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