

Energy Balance, Body Size, and Cancer

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ABSTRACT

Increased energy intake and physical inactivity have been shown to heighten the risk of breast, large bowel, and other cancers. Large body size and fatness, as measured by adult stature, body weight and body mass indices, are positively related to a variety of cancers, including breast, colorectum, prostate, endometrium, kidney, and ovary, as well as to total cancer incidence or mortality in many investigations, although conflicting reports exist. Adult weight gain has also been specifically implicated in a few etiologic studies of breast and large bowel cancer. Furthermore, increased birthweight and childhood stature have been linked to increased risk of leukemia, lymphoma, osteogenic sarcoma, and central nervous system malignancies between infancy and young adulthood. Greater body weight also adversely affects breast cancer survival. These findings are complementary and support a role for positive energy balance in promoting human carcinogenesis. Potential mechanisms are discussed.

I. INTRODUCTION

More than a century after Sir Percivall Pott noted the unusually frequent occurrence of scrotal tumors among chimney sweeps in late eighteenth century England, Rabagliati recorded some thoughts and observations concerning more common everyday events in the treatise entitled "Air, food and exercises."¹ Therein he summarily concluded that, "Overfeeding is the predisposing cause of cancer," (p.398). Subsequent animal experiments such as those of Rous,² Bischoff,³ and Tannenbaum^{4,5} provided conclusive evidence for the important role of food and energy intake in carcinogenesis. Since then, many investigations of humans have examined the relationship between cancer and both energy intake and body weight. These include descriptive cross-sectional or ecologic studies, case-control investigations, and the generally larger cohort studies. In all, over 150 such investigations involving a broad range of cancer sites have been conducted in this field, which, given the rising prevalence of overweight in most modern societies, will likely become increasingly important in the years ahead.

This review summarizes relevant research dealing with energy balance and body size (including stature and birthweight) as they relate to human cancer, and attempts to clarify some of the complex relationships involved.

II. ENERGY BALANCE AND CANCER

The importance of energy balance — that is, energy intake

minus energy expenditure — in carcinogenesis has been consistently demonstrated since early animal experiments conducted in the 1930s and 1940s.^{4,5} These studies, which have recently been reviewed,⁶ show that rodent tumor incidence increases with increasing energy intake and body weight over a wide range of intake. 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, hematopoietic elements, 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. Although no similar human experiments of energy restriction exist, observational studies of energy intake and physical activity levels are available which provide evidence that these two major (and modifiable) components of energy metabolism may influence the development of cancer in humans.

A. Energy Intake and Cancer

Individual caloric intake is usually assessed through dietary questionnaires of which there are several kinds, including 24-h recall surveys, food frequency questionnaires, and the more complete diet history methods.⁷ Most commonly used in epidemiological research are food frequency questionnaires^{8,9} which can, in most cases, only estimate energy intake (some less comprehensive instruments cannot accomplish even this because of the limited type and number of foods surveyed). The period of interest varies among these methods, ranging from the distant past for some histories, to "usual" intake (e.g., throughout adulthood or in the past year), or to the present (i.e., yesterday or this past week).¹⁰ Although repeated multiple-day dietary diaries offer a more valid measure of energy consumption, they are difficult to administer and time-consuming to process, and are, therefore, utilized in relatively few epidemiologic or clinical studies. Advantages and shortcomings of several available methods for measuring individual energy intake have been previously discussed.^{7,11,12} Ecological investigations, in contrast, usually employ per capita food "disappearance" data such as those available for most nations from the Food and Agriculture Organization¹³ or from other

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national data sources.¹⁴ Analysis of such data, however, assumes an average intake within each population and does not take into account food wastage which is particularly common in industrialized countries.

Investigations of the relationship between energy intake and cancer in humans include four cross-sectional and six case-control studies. An international correlation study by Armstrong and Doll¹⁵ demonstrated that countries exhibiting increased availability of total per capita food calories experienced greater cancer incidence and mortality compared to lower-calorie nations. Site- and sex-specific correlation coefficients (r 's) based upon concurrent food and cancer data for 33 countries were presented in the report which demonstrated significant associations between total calories and cancer of the breast, colon, rectum, uterus, and kidney in women (r 's 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 's of 0.60, 0.75, 0.55, and 0.56, respectively). Similarly, in the cross-sectional study of colorectal cancer mortality in Hong Kong by Hill et al.,¹⁶ a greater than twofold rate increase was observed for persons in the highest of three family income categories compared to the lowest income group (in males, 26.7 vs. 11.7 per 100,000). This was related to increased consumption of all foods among high income individuals, including estimated daily caloric intake; that is, for adult males 3900 kcal vs. 2700 kcal in the low income population. In contrast to these two studies, Kato et al. failed to demonstrate any correlation between energy intake and breast or ovarian cancer mortality in Japan.¹⁷

Most case-control studies of diet and cancer have not evaluated total caloric intake, in part because of limitations inherent in the dietary methods employed. Of the six studies assessing the role of energy intake in cancer, four demonstrated a positive association between total caloric intake and cancer risk and two showed no clear relationship. In the study by Miller et al. which reported an association between dietary fat and breast cancer,¹⁸ mean daily caloric intake of breast cancer cases was also slightly (albeit significantly) higher than that of controls based on a 24-h recall. Caloric intake estimated from a dietary history questionnaire and 4-d diary records showed somewhat reduced case-control differences. The association was stronger among postmenopausal women than among premenopausal women. No clear dose-response relation was demonstrated for caloric intake, however, with risk ratios of 1.3 and 1.1 for premenopausal women of moderate or high (>2500 kcal) daily intake compared to the \leq 2000 kcal group, respectively. Among post-menopausal women, risk ratios of 1.0, 0.8, and 1.2 were obtained for three quartiles compared to the group ingesting less than 1500 kcal daily. In contrast to this study, Jain et al. 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.¹⁹ Relative risks of 1.5 and 1.8 were demonstrated among men for the medium (2485 to 3255 kcal/d) and high (>3255 kcal/d) intake groups compared to the low

intake group (<2485 kcal/d). The corresponding risk ratios among the women were 1.6 and 2.2., using 1760 and 2360 kcal as tertile boundaries.

An investigation of large bowel cancer by Bristol et al.²⁰ showed substantially greater calorie intake for cases (mean = 2370 kcal) than for controls (2046 kcal), with relative risk increasing from 1.0 (<1936 kcal) to 2.2 and 23.0 (>2486 kcal). Lyon et al. also found higher caloric intake among colon cancer cases compared to controls.²¹ Relative risk ratios of 1.0, 2.5, and 2.5 were observed for <1900 kcal to >2600 kcal in men; 1.0, 2.0, and 3.6 for <1300 kcal to >1800 kcal in women. Adjustment for differences in body mass index did not alter these findings for energy intake. In contrast, two other studies of colorectal cancer demonstrated negligible case-control differences in caloric intake.^{22,23} Stemmermann et al. observed slightly lower and higher mean calorie intake among colon and rectum cancer cases, respectively, compared to controls.²² Similarly, small case-control differences, inconsistent across sexes, were reported for energy intake by Kune et al. in their in-depth evaluation of dietary factors and large bowel cancer.²³

These studies provide some evidence for a positive relationship between energy intake and cancer of the breast and possibly colorectum. It should be kept in mind that in none of the above investigations were data regarding energy expenditure, and, therefore, true energy balance, available. In one of the studies, however, adjustment for differences in body mass index had no effect on the calorie results.²¹ By contrast, the one study in which body size was also analyzed separately demonstrated a stronger association between breast cancer and body mass index²⁴ than for energy intake¹⁸ (see "Body Weight, Body Mass Indices and Adult Cancer" in the following). Therefore, given the paucity of such data, it is not possible to determine the independence of the effects of increased energy consumption from those of greater body mass or fatness.

B. Physical Activity and Cancer

Energy used for physical activity accounts for approximately 15 to 40% of total energy expenditure and energy intake in the general population.²⁵ Substantial variation in this parameter exists, however, between persons of different ages, occupations, and leisure activity, in contrast to basal (or resting) metabolic rate which is more a linear function of lean body mass and accounts for approximately 50 to 75% of energy expenditure.²⁵ Several physical activity questionnaires, covering leisure and occupational activity, are currently available and have been reviewed recently.²⁶ Work-related physical activity can also be estimated and categorized using published standards.²⁷ More accurate and complicated methods for measuring total energy expenditure exist, including direct²⁸ or indirect²⁹ calorimetry, or the double-labeled water technique,³⁰ but are not commonly used in studies of cancer. There are 11 reported investigations of physical activity and cancer, most

of these having examined either occupational histories or involvement in athletics. Unfortunately, in only one of these studies³¹ is information concerning energy intake available, permitting some assessment of energy balance. The studies do, however, provide some information with respect to the possible effects of the second major source of energy expenditure on cancer.

Several studies demonstrate an inverse relationship between occupational physical activity, based on job classification, and the development of malignancy. Siversten and Dahlstrom,³² in a historically interesting report, showed that the death rate from carcinoma was higher among the unemployed, and inversely related to estimated occupational "muscular activity." The authors attributed their observations to metabolic products of deficient muscular activity which "altered body fluids" and, therefore, adult epithelial tissue. The effect of age and the tendency for ill individuals to be unemployed or reduce their activity were not, however, adequately addressed. Among railroad workers, Taylor et al.³³ demonstrated approximately one third lower cancer death rates for men involved in heavy manual labor compared to less active clerks and switchmen. In three more recent studies, the risk of colon cancer was increased by between 30 and 100% among men employed in sedentary occupations.³⁴⁻³⁶ In the study by Garabrant et al.,³⁴ colon cancer risk increased linearly with decreasing levels of job activity across several socioeconomic and racial groups. The observed association was particularly strong for malignancies involving the descending colon. Vena et al.³⁵ gathered more detailed information concerning work histories and found more men who had worked in sedentary or light activity occupations (and for longer periods) among colon cancer cases than among controls. Similar but less striking results were obtained in the much larger follow-up investigation of over one million Swedish men conducted by Gerhardsson et al.³⁶ In none of these three studies was rectal cancer associated with job inactivity.

Reporting findings from four separate analyses concerning cancer and physical activity, Paffenbarger et al.³⁷ demonstrated a marginally increased risk of smoking-adjusted cancer mortality among low to moderate physical activity dockworkers (i.e., jobs at approximately 1100 kcal/d expenditure) compared to high energy output jobs (1900 kcal/d). This was explained primarily by lung cancer (relative risk 1.7 among less active workers). An add-on cohort of workers showed a similar association for lung and prostate cancer, but a weak direct activity-colorectal cancer relation. Nonrecreational inactivity, and possibly sedentary occupation, were also associated with greater total cancer incidence (relative risks = 1.8 and 1.3, in men and women respectively, for inactivity versus very active) followed up from the first National Health and Nutrition Examination Survey.³¹ The association was stronger for large bowel and lung cancer in men, and breast (postmenopausal) and cervical cancer in women. The data also suggested that recreational exercise may have a protective role in prostate cancer.

Although the findings were not changed by adjustment for caloric intake, body mass index, smoking status, reproductive, or various other factors, there was a stronger cancer-activity relationship among leaner persons. In addition, adjustment for general health status and recent hospitalization did not alter the findings in this study.

The study of athletes, another approach to investigating the relationship between cancer and physical activity (or more specifically, fitness), has yielded conflicting results. One case series found gymnasts or past athletes underrepresented in a retrospective study of cancer of the stomach.³⁸ In contrast, a high rate of cancer mortality was discovered postmortem in a series of 780 athletes.³⁹ These early studies lacked control groups, and may have suffered both from biased samples and inadequate consideration of age. A retrospective cohort study by Polednak⁴⁰ based on death certificates and athletic status in college showed a small excess of cancer mortality, particularly for cancer of the prostate, among Harvard varsity athletes compared to either athletes not having received a "letter," or to students who had applied for, but did not receive, a gymnasium locker. The author could not rule out other confounding effects such as smoking or body size, however. In a similar investigation by Frisch et al.,^{41,42} female college alumni who had actively participated in one or more team sports during college reported less cancer of the breast, uterus (including cervix), and ovary after college than did nonathlete alumni. Nonathletes experienced approximately twice the rate of breast cancer compared to athletes and 2 1/2 times that of other reproductive system cancers. This association, which persisted after adjustment for several breast cancer risk factors, was evident primarily in women 50 to 70 years old. The number of cancers in this study was, however, small: 69 breast, 37 all others combined. In a previously mentioned report,³⁷ greater participation in sport activities during college conferred some protection against rectal (but not colon) cancer, and was directly related to prostate cancer in a cohort of alumni. Adult exercise, in contrast, which had previously been shown to progressively reduce all-cause and cardiovascular mortality among alumni, also demonstrated a similar association with cancer mortality which was primarily restricted to lung and prostate cancer. Rates of large bowel cancer were higher among men expending more energy in their leisure, however, a finding in conflict with four of the above studies.^{31,34-36}

Although only a limited number of investigations have been published in this area, they generally support the notion that higher levels of physical activity may be protective against the development of cancer. Data are most available for colon, lung, and total cancer in men, and there is some evidence for a protective role in breast and endometrial carcinoma as well. Experimental data for rodents also demonstrate an anti-tumorigenic effect (in the mammary gland and colon) of regular physical activity.⁴³⁻⁴⁵ In one of these studies, combining exercise with caloric restriction led to even greater inhibition of

mammary tumorigenesis than from exercise alone.⁴³ Although reduced body weight was observed in the exercise groups of these experiments, evidence from three of the above epidemiological studies suggests that the effects of physical activity on carcinogenesis may not be merely due to differences in body weight.^{31,37,42} In one, former female athletes, while taller and leaner than their nonathlete counterparts, developed fewer breast and other reproductive system cancers, and this cancer-athletic status association remained strong after adjustment for body mass index and other factors.⁴² Relative risk estimates for activity levels were similarly unchanged after adjustment for body mass index in two other reports,^{31,37} although as mentioned, the activity-cancer relationship was greater among leaner individuals in one of these studies.³¹ These investigations raise the possibility that increased physical activity may act through mechanisms (e.g., hormonal,⁴⁶ immunological,⁴⁷ or physical⁴⁸) not directly related to body weight or fatness.

III. BODY SIZE AND RISK OF CANCER

Many investigators have examined the relationship between cancer and various measures of body size in humans, and interest in this area continues to increase. Although most of the reports concern hospital- or population-based case-control studies, several correlation and cohort studies exist which investigated cancer incidence or mortality rates in relation to body size. The studies involve several adult and childhood cancers. While many early investigations focused on absolute body weight or weight relative to some population standard (some through the use of clinical practice or life insurance policy records), most later studies stressed body mass indices. Stature (i.e., standing body height) has also been examined in many of the same investigations. In addition, birthweight has been related to the subsequent development of cancer.

Body size is affected by energy balance throughout life. Energy intake in excess of optimal requirements leads to accelerated growth and increased fatness from infancy through adolescence, and produces children and adults who are taller and more overweight than they would otherwise be.⁴⁹ Positive energy balance in adulthood results in increased adipose (or lean) tissue stores.^{25,50} Body size is also known to "track" from birth through adulthood, to some degree. For example, postnatal weight and weight gain are directly related to birthweight.⁵¹ Infants of higher birthweight have been shown to retain their advantage of weight and fatness over their lower birthweight counterparts, and gain more weight (absolute and relative) through infancy and childhood.⁵² Similarly, obese children and adolescents, who are more likely to become obese adults,⁵³ are taller than their non-obese peers. These and other descriptive data suggest that stature and fatness are correlated.⁵⁴ Such observations are consistent with a common influence of positive energy balance on body size throughout life.

Body size can be measured and described using various

anthropometric dimensions including body weight and stature. Body weight (BW) is composed of lean and fat mass, and is to a large extent dependent upon stature. Although absolute weight primarily measures overall size, it also reflects fatness, particularly in adulthood. Stature (S) is determined primarily by heredity and early nutrition, and remains relatively fixed after growth cessation late in the second decade of life; this anthropometric dimension is, therefore, one important marker of early (i.e., pre-adult) nutritional exposure, including energy intake relative to requirements. Body mass indices (BMIs), or weight divided by stature raised to some exponent, provide measures of BW corrected for S.⁵⁵ The most commonly used index is weight/stature², also known as the Quetelet index, after the 19th century Belgian statistician. This particular formula or, for example, weight/stature^{1.5} which has been used for women, have generally been found to correlate more highly with weight and fatness and be independent of height in many populations, compared with other indices such as weight/stature or weight/(stature³).^{56,57} While it has been pointed out that these indices represent both lean and fat mass,^{58,59} in general, most of the variability in BMIs within populations is due to differences in the amount of adipose tissue.^{56,57} In this review, the term relative body weight (RBW), as opposed to BMI, is used to connote weight relative to that of other persons of the same age, sex, and height in the study population or to some outside population standard (e.g., Metropolitan Life Insurance Company weight-for-height tables⁶⁰). Alternative measures of body fat and frame size have been less commonly studied (e.g., skinfold thickness or elbow breadth). Similarly, more accurate but technically demanding and time-consuming methods of determining body composition, such as underwater weighing,⁶¹ are infrequently used in clinical or epidemiological research. More exhaustive discussions of anthropometry and the determinants of body size can be found elsewhere.^{62,63}

A. Body Weight, Body Mass Indices and Adult Cancer

1. Correlation Studies

BW has been correlated with cancer incidence or mortality rates in one study of secular trends in Japan and three international studies. Dramatic increases in body weight (and height) in Japan between 1950 and 1974 were related to higher cancer rates during the same period by Kagawa.⁶⁴ For example, the BW of 12-year-old girls increased from 32.2 to 41.0 kg at the same time breast and colon cancer mortality rates increased 77 and 78%, respectively. Gray et al. demonstrated correlation coefficients ranging from 0.56 to 0.75 for the association between BW and breast cancer rates.⁶⁵ In a unique study by Micozzi,⁶⁶ the correlations of weight at various ages during childhood and adolescence with adult breast cancer rates increased with childhood age and was strongest for weight in late adolescence. The correlation coefficients ranged from 0.48 at age 6 years to 0.75 at age 18. Breast, uterine corpus, ovary,

central nervous system, rectum, and pancreas cancer were significantly correlated with BW among women in another recent ecologic investigation conducted by Albanes and Taylor;⁶⁷ correlation coefficients ranging from 0.42 to 0.60. By contrast, in men this was true only for rectal cancer ($r = 0.49$).

2. Case-Control Studies

There are more than 70 case-control investigations that have assessed the relationship between BW, BMIs, or RBW, and site-specific cancer. These studies are summarized in Table 1. Eighty percent of the studies examined weight relative to height, while approximately half involved only absolute body weight. Cancers of the breast, endometrium, kidney, ovary, prostate, and colorectum have been most frequently studied. A positive association between BMI or RBW was demonstrated in two thirds of the studies which have looked at these factors. The same proportion of BW investigations were positive. The vast majority of breast, endometrium, ovary, and renal cancer investigations demonstrated positive associations. With the exception of a few studies which implicated leanness as a cancer risk factor, most other studies reported either no association or an association which differed between subgroups of subjects. For example, several studies suggest that leanness increases breast cancer risk premenopausally, while overweight does so after the menopause.^{24,74,79,87,89,91,95} Even though BW or BMI categories and their associated risk estimates varied among the studies, relative risks of two or more were commonly observed for the highest compared to the lowest weight or BMI groups, often in a dose-response fashion. Adjustment was made for potential confounding factors in many of the investigations. It is of note that in relatively few of the reports 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. (Self-reported weight or that derived from driver's license records is reasonably accurate,^{138,139} although the potential for a bias toward underreporting by overweight individuals may exist.¹⁴⁰) Overall, these case-control studies support a positive relationship, particularly among women, between adult weight and fatness and cancer.

3. Cohort Studies

Prospective studies that have investigated the relationship between BW or obesity and cancer incidence or mortality are presented in Table 2. Of the eight studies of cancer incidence, four involved multiple sites and four investigated breast cancer only. The 13 mortality studies included 8 of total or multiple site cancer mortality only, one assessed site-specific and total cancer mortality, and four assessed site-specific mortality only. There was one study of cancer prevalence in women. In addition, some studies evidenced a positive association with cancer for weight gain in adulthood or skinfold thickness,^{95,150,155,162,167} the latter being a more specific measure of body fat. Overall, the studies are supportive of an association between obesity and cancer, while also pointing to increased rates of cancer for some sites among the most underweight individuals, primarily in men. Several factors relevant to the pathogenesis of human cancers should be considered when evaluating these prospective investigations, however. These include potential confounding by known cancer risk factors (e.g., cigarette smoking), the effects of antecedent, subclinical illness on BW, and competing causes of death among overweight individuals.

Analyses of life insurance company records such as the study of Dublin¹⁴¹ represent some of the earliest documented evidence concerning the association between BW and cancer mortality in humans. In this study, the mortality experience of nearly 200,000 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 to 50% underweight. Mortality rates were unadjusted for differences in age between weight categories, however. Tannenbaum has reviewed six of these early studies which focused on total cancer mortality, all but one of which were supportive of the hypothesis that RBW is positively related to cancer mortality.¹⁶⁸ In the Build and Blood Pressure Study (BBPS),¹⁴² as well as its successor, the Build Study (BS),¹⁴³ higher cancer mortality ratios were observed for the most overweight women, and in the latter study, among men and women more than 14% underweight. The mortality ratios reported,

Table 1
Case-Control Studies Relating Body Size to Adult Cancer

First author/ year	No. of cases	Factor(s) studied	Findings	Ref.
<i>Colorectum</i>				
Wynder 1969	300	RBW	No case-control difference in RBW among Japanese.	68
Dales 1979	99	BW S	"Slightly higher" BW in cases. "Little" difference in S. Data not presented.	69
Potter 1983	155	BMI	RR = 1.0, 1.3, and 0.8 for categories <22 to >25 (colon). RR = 1.0, 0.6, and 0.4 (rectum).	70
Bristol 1985	50	BW S	Male and female cases weighed less but were slightly taller than controls.	20
Berry 1986	53	BMI	No difference between carcinoma or polyp cases (means 26.5 vs. 25.4) and controls (26.0).	71

Table 1 (continued)
Case-Control Studies Relating Body Size to Adult Cancer

First author/ year	No of cases	Factor(s) studied	Findings	Ref.
Lung Lee 1983	80	S	RR = 1.0, 3.2, and 3.7 for three categories of S in smoking men. RR = 1.0 and 1.8 for two categories of S in smoking women. Association also seen in nonsmokers.	72
Breast Wynder 1960	632	RBW	Cases more likely to be "stocky" or obese.	73
de Waard 1964	300	RBW	Postmenopausal cases more overweight than controls; RR = 1.3 and 1.6 for obesity and obesity plus hypertension; opposite trend in premenopausal women.	74
Valaoras 1969	758	BW BMI S	RR = 1.0, 1.5, 1.9, 1.7, 1.9, 1.7, and 1.8 for BW categories <55 to ≥85 kg. RR = 1.0, 1.3, 1.6, 1.2, 1.3, and 1.7 for BMI categories <22 to ≥30. RR = 1.0, 1.3, 1.4, 1.6, and 2.4 for S categories <155 to ≥170 cm	76
Lin 1971	213	BW S	RR = 1.0, 1.6, 1.5, 2.5, and 2.0 for BW categories <45 to ≥60 kg. RR = 1.0, 0.9, 0.6, and 1.3 for S categories <154 to ≥158 cm. Increased effect among women ≥50 years old.	77
Mirra 1971	536	BW BMI S	RR = 1.0, 1.6, 2.3, and 2.5 for BW categories <55 to ≥75 kg. RR = 1.0, 0.9, 1.5, and 1.6 for BMI categories <22.0 to ≥27.0. Positive association for S (data not given). Associations observed only among women ages ≥50.	78
Ravnihar 1971	772	BW S	RR = 1.0, 1.2, 1.2, 1.1, 1.1, 1.5, and 1.3 for BW categories <55 to ≥80 kg. RR = 1.0, 0.8, 1.0, 1.2, and 1.1 for S categories <155 to ≥170 cm.	79
Stavraky 1974	373	BMI	RR = 0.7 for high BMI category (3.6 lb/in ² vs. <2.5) in premenopause. RR = 1.0 in postmenopause.	80
Adami 1977	179	BW BMI S	No significant case-control differences in mean BW (66.3 vs. 66.0 kg) or BMI (25.5 vs. 25.4), in postmenopausal women. Opposite trend in premenopausal women also not significant. Used measured BW and S for controls, self-reported BW for cases.	81
de Waard 1977	1006	BW BMI S	RR increased with BW and S (up to 2.0 and 1.6, respectively, for the highest categories ≥70 vs. <60 kg; ≥165 vs. <160 cm), especially in older age groups. No BMI association. Cases with positive axillary nodes were heavier than those without nodal involvement.	82
Soimi 1977	122	BW, BMI S	No significant case-control differences for either BW or BMI. RR = 1.0, 1.1, 1.0, and 1.6 for S ≤159 to ≥170 cm. Limited age range (41 to 60 years) and no analysis by menopausal status.	83
Staszewski 1977	900	BW BMI S	RR = 1.0, 1.2, 1.3, and 1.5 for BW <60 to ≥80 kg. RR = 1.0, 1.1, 1.2, and 1.4 for BMI <24 to ≥30. RR = 1.0, 1.1, 1.1, and 1.6 for S <160 to ≥170 cm. Stronger association for BW and BMI in 50 to 69 year olds. S stronger in 25 to 49 year olds.	24
Choi 1978	400	BW S	Increased mean BW for postmenopausal cases, especially for older women and BW at time of menopause (71.7 vs. 60.6 kg for ages ≥70 years). Decreased BW for premenopausal cases (59.6 vs. 63.5 kg). Postmenopausal cases also taller.	84
Hirayama 1978	400	BW S	RR = 1.0, 4.8, 4.5, and 12.4 (postmenopausal) and 1.0, 1.3, 2.1, 3.0 (premenopausal) for obesity categories: thin, ordinary, slightly obese, obese. Independent positive associations for BW and S.	85
Wynder 1978	785	BW, BMI S	No case-control differences for BW, BMI or S among pre-, peri-, or postmenopausal women. Age not taken into account.	86
Brinton 1979	405	BW S	RR = 1.0, 1.2, 1.3, and 1.5 for BW <125 to ≥155 lb. RR = 1.0, 1.4, 1.0, and 1.3 for S <62 to ≥66 in.	87
Paffenbarger 1980	1403	BMI S	RR = 1.0, 1.3 and 1.4 (postmenopausal) and 1.0, 0.9 and 0.7 (premenopausal) for categories <21.5 to ≥24.5. Increased S in premenopausal cases. Similar trends for BMI at (and BW gain since) age 20.	88
Ross 1980	138	BW S	RR = 1.0, 1.2, and 1.7 for BW <125 to ≥150 lb. RR = 1.0, 1.1, and 1.5 for S <63 to ≥65 in.	89
Kelsey 1981	332	BW	RR = 1.6 for postmenopausal women >56.8 kg. RR = 0.4 for premenopausal women >75 vs. ≤56.8 kg.	90
Brinton 1983	1197	BW BMI S	RR = 1.0, 1.1, 1.3, and 1.4 for BW <56.6 to ≥70.1 kg. RR = 1.0, 1.1, 1.1, and 1.3 for BMI <22 to ≥26. RR = 1.0, 1.1, 1.2, and 1.3 for S <157.5 to ≥167.6 cm.	91
Helmrich 1983	1185	BMI	RR = 1.0, 0.5, 0.7, and 0.5 for BMI <30 to ≥40 lb/in ² (premenopausal). RR = 1.0, 1.5, 1.6, and 1.3 in postmenopause.	92
Brisson 1984	362	BW	RR = 1.0, 1.3, 2.3, and 2.7 for categories <55 to ≥75 kg. Effect in pre- and postmenopausal women; inverse association with S.	

Table 1 (continued)
Case-Control Studies Relating Body Size to Adult Cancer

First author/ year	No. of cases	Factor(s) studied	Findings	Ref.
de Waard 1984	296	BW, BMI S	RR = 1.0, 1.2, 1.4, and 1.2 for BW <60 to \geq 80 kg. RR = 1.0, 1.3, 1.3, and 1.5 for BMI <23 to \geq 31. RR = 1.0, 0.9, 0.9, and 1.0 for S <155 to \geq 170 cm. Body surface area also positively related.	93
Talamini 1984	368	BMI	RR = 1.0, 1.5, and 1.9 for <25 to \geq 30 (all ages). RR = 1.0, 1.4, and 2.1 for postmenopausal women only.	94
Hislop 1986	846	BW, BMI S	No consistent association for BW or BMI although inverse and positive relations suggested for BW and S in pre- and postmenopausal women, respectively. Subjective reports of BW relative to age peers showed "heavier" children and teens at reduced risk of premenopausal cancer.	95
Lubin 1985	1065	BW, BMI S	No other differences for S, recent adult or age 18 BW or BMI. RR = 1.0, 2.2, 2.4, and 3.0 for BMI \leq 19 to >27 (cancer vs. neighborhood controls).	96
Kolonel 1986	272	BW, BMI S	RR = 1.0, 1.1, 1.7, and 1.6 for BW quartiles in postmenopausal Japanese. No association in Caucasians. RR = 1.0, 1.1, 1.9, and 1.1 for BMI. Strong association for shoe size also.	97
Wysowski 1986	133	BW, BMI S	BW and S (current, at menopause, and 1 year before diagnosis) were slightly greater in cases. No difference for BMI.	98
La Vecchia 1987	1108	BMI	RR = 1.0, 1.4, 1.4, and 1.6 for BMI <20 to \geq 30. Strong association premenopausally.	99
Schatzkin 1987	529	BMI	RR = 1.0, 0.9, and 1.2 for BMI \leq 24 to \geq 30 (premenopause). RR = 1.0, 1.3, and 2.5 (postmenopause).	100
<i>Breast</i> Male				
Casagrande 1988	75	BW, BMI S	RR = 1.0, 1.7, 2.0, 2.1, and 5.5 for BW (age 30) <60 to \geq 90 kg. Cases taller and heavier (at age 30, 5 years earlier, and maximum).	101
<i>Cervix</i> Parazzini 1988	39	BMI	RR = 1.0, 2.2, and 4.8 for BMI <25 to \geq 30. Adenocarcinoma only.	102
<i>Endometrium</i> Palmer 1949	957	RBW	75% of uterine corpus cases overweight. More extreme overweight among corpus cases.	103
Wynder 1966	112	RBW S	RR = 9 for women over 50 lb overweight at age 25 to 29 (RR = 10 at age 50 to 59). Cases also had greater adult BW gain. RR increased up to sevenfold from short (5 ft 2 in.) to tall (\geq 5 ft 6 in.) women.	104
Fox 1970	300	RBW	No case control difference in presence of "obesity" (34 vs. 31%).	105
La Vecchia 1982	173	BMI	RR = 1.0, 1.3, 2.0, 5.1, and 19.1 for BMI <20 to \geq 35. Association stronger among nonestrogen users.	106
Kelsey 1982	167	BW	RR = 1.0, 1.3, 1.3, and 2.3 for categories \leq 56.9 to >75 kg. Similar trend for BMI (not presented by authors).	107
Henderson 1983	127	BW	RR = 1.0, 1.5, 2.0, 9.6, and 17.7 for categories <59 to >86.1 kg. Similar trends for BMI, and for BW at age 18.	108
La Vecchia 1984	283	BMI	RR = 1.0, 1.6, 3.3, and 7.6 for categories <20.0 to >30.0 in postmenopausal women. RR = 1.0, 1.5, 3.9, and 20.3 for same categories in premenopausal women.	109
Jensen 1986	414	BW RBW S	Increased mean BW, RBW and S among cases in nearly all age groups (35 to 95).	110
La Vecchia 1986	206	BMI S	RR = 0.4, 1.0, 1.8, and 3.1 for BMI <20 to \geq 30.	111
Lawrence 1987	200	BW	RR = 1.0, 1.1, 2.0, and 5.7 for <140 to >190 lb (nonsmokers). RR = 1.0, 0.8, 1.1, and 1.4 in smokers.	112
<i>Ovary</i> Wynder 1969	158	RBW	Little case-control difference in RBW.	113
Annegers 1979	116	RBW	RR = 1.4 for obesity (\geq 30% above ideal weight).	114
Casagrande 1979	150	BMI RBW	RR = 2.1 for obesity (\geq 20% above ideal weight), with a "very significant" positive relation for BMI as well.	115
Byers 1983	274	BMI	RR = 1.0, 1.0, 0.9, 0.6, and 0.7 for BMI <21.5 to >30.0. Inverse association suggested for 50 to 79 year old women.	116

Table 1 (continued)
Case-Control Studies Relating Body Size to Adult Cancer

First author/ year	No. of cases	Factor(s) studied	Findings	Ref.
Cramer 1984	215	BW, BMI S	RR = 1.0, 1.2, 1.2, and 1.5 for BMI <22 to ≥29. Cases also heavier but not taller.	117
Tzonou 1984	150	BW, BMI S	RR = 1.0, 0.8, 1.1, 1.1, 1.4, and 1.8 for BW for ≤54 to ≥75 kg. RR = 1.0, 1.1, 0.9, and 1.8 for S ≤154 to ≥165 cm. No reported association for BMI.	118
<i>Prostate</i> Wynder 1971	300	RBW S	No significant difference in RBW or S between cases and controls.	119
Graham 1983	260	BW, BMI S	No case-control differences reported. Data not presented.	120
Talamani 1986	166	BW, BMI S	RR = 1.0, 2.3, and 3.0 for BW <65 to >95 kg. RR = 1.0, 2.5, and 3.9 for BMI <23 to ≥28. No association for S (data not presented).	121
Kolonel 1988	452	BW, BMI S	No case-control differences in any of the factors.	122
<i>Kidney</i> Wynder 1974	202	RBW	Greater proportion of cases (29 vs. 10%) with RBW ≥125% (among women only). Also, more underweight persons among controls.	123
McLaughlin 1984	495	BMI	RR = 1.0, 1.2, 1.7, and 2.3 for categories ≤21.6 to >26.2 in females. RR = 1.0, 0.9, 0.8, and 1.3 for categories ≤23.6 to >27.9 in males. Positive association observed in older ages and for weight gain since age 20 (females).	124
Maclure 1985	55	BMI	RR = 3.0 for high vs. low quintile in women. RR = 2.0 in men.	125
Goodman 1986	267	BMI	RR = 2.7 for categories >28.0 vs. <24.0 for men. RR = 2.4 in women.	126
Asal 1985	315	BMI	RR = 2.2 for high vs. low quintile for BMI at age 20 in men; RR = 2.7 in women; RR = 3.0 for men if current BMI used.	125
Yu 1986	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. Higher RR for BMI 10 years prior to study and at age 20.	128
<i>Melanoma</i> Holman 1984	276	BMI	RR = 1.0, 1.3, 1.3, and 0.9 for BMI <19 to ≥31. Study of females only.	129
<i>Meningioma</i> Bellur 1983	176	RBW	RR = 4.2 for "obese" women; p < 0.001. No significant difference among men.	130
Jacobs 1986	203	RBW	Cases less likely to be obese (≥10% above ideal BW) than sample U.S. population.	131
<i>Thyroid</i> McTiernan 1987	182	BW	RR = 1.0, 1.6, 2.5, 2.8, and 2.2 for BW ≤52 to ≥74 kg. BW 5 years before study.	132
<i>Hodgkin's Disease</i> Hancock 1976	107	S	Cases significantly taller than controls, males and females. S measured postmortem.	133
Paffenbarger 1977	45	BMI S	RR = 1.9 for "obesity" ("Ponderal index" <12.9). No S association (data not shown).	134
<i>Choriocarcinoma</i> Buckley 1988	75	BW, BMI S	RR = 1.0, 2.9, and 3.1 for BW >141 to <120 lb. RR = 1.0, 2.3, and 3.2 for BMI >23.5 to <20. RR = 1.0, 0.7 and 1.2 for S >67 to <63 in. Protective effect for regular exercise also.	135
<i>Multiple Sites</i> Damon 1960	910	BW, BMI S	Only uterine corpus and multiple cancer cases found to be heavier (BW) and "stockier" (BMI) than controls. Breast, cervix, and ovary cases were more similar to controls. No S differences. Endomorph somatotype more common among corpus cases.	136
Higginson 1966	433	BW	Female stomach and colorectal cancer cases taller and heavier (BW) than controls. No association for males.	137

Note: BW = body weight; BMI = body mass index (weight/height², unless otherwise specified); RBW = relative body weight; S = stature; and RR = relative risk.

Table 2
Cohort Studies Relating Body Size to Adult Cancer

First author/ ref./year	Study population	Factors studied	Findings									
<i>Total Cancer</i>												
Dublin ¹⁴¹ 1932	Approximately 192,000 males, ages ≥45	RBW 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 ¹⁴² 1959	Approximately 4,900,000 males and females ages 15—69; 133,000 deaths	RBW Mortality ratio (%)	RBW (%) Ratio	60—85 116	84—110 100	111—134 100	135—154 112	155—174 112	≥175 105 138			
Age-adjusted mortality ratios for both Society studies based on expected deaths from all causes; BW reduction associated with lower total mortality.												
Society of Actuaries ¹⁴³ 1979	Approximately 4,200,000 males and females ages 15—69; 106,000 deaths	RBW Mortality ratio (%)	RBW (%) Ratio	65—75 130	-85 109	-95 89	-105 84	-115 85	-125 93	-135 94	-145 93	-155 133
Sorlie ¹⁴⁴ 1980	5,209 males and females, ages 30—62; 1,295 deaths	RBW Mortality	Slightly inverse between 6-year cancer death rate and RBW in men. Inverse relation primarily among smokers and during the first 12 years of follow-up for total mortality. Data for cancer not shown for women, and data presented graphically only.									
Wallace ¹⁴⁵ 1982	5,565 males and females, ages 20—94; 131 cases	BMI 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. Greatest difference seen for smoking-related cancers and after 2 years of follow-up.									
Jarrett ¹⁴⁶ 1982	18,393 males, ages 40—64; 1,722 deaths	BMI Mortality	BMI quintiles Rate/1,000/year	(≤22.4)	Q1 3.2	Q2 2.6	Q3 3.0	Q4 3.0	Q5 3.0	(>27.0)		
Early rate (<2 years)												
Late rate (2—10 years)												
Excess total mortality among lean individuals observed only at ages ≥55 years.												
Avons ¹⁴⁷ 1983	7,591 males, ages 43—53; 908 deaths	BMI Mortality	BMI quintiles Rate/1000/year	(<23.0)	Q1 5.2	Q2 2.3	Q3 1.9	Q4 1.9	Q5 2.4	(>28.5)		
Rate for BMI change												
(Q1—Q5: <0.5 to >6.5)												
No trend for BMI at age 25.												
Rhoads ¹⁴⁸ 1983	8,006 males ages 45—68 223 deaths	BMI Mortality	BMI quintiles Rate/1,000/year	(<21.2)	Q1 3.9	Q2 3.2	Q3 2.7	Q4 1.6	Q5 2.2	(>26.3)		
Rate for BMI at age 25												
Excess cancer deaths in lean men restricted to those who lost BW after age 25.												
<i>Colorectal</i>												
Phillips ¹⁴⁹ 1985	25,493 males and females ages 35 + 158 deaths	BMI Mortality	RBW (%) RR	85—99 1.6	100—109 1.0	110—124 1.3	≥125 1.6					
Stronger association for rectal cancer, and colon cancer in men.												
<i>Lung</i>												
Garn ¹⁵⁰ 1983	2,381 males ages 45—75 223 deaths	BW BMI Mortality	Fatness level Weight Weight/Height	Low 5% (lean) 6.2%	Medium 15—85% 4.2%	High >85% (obese) 3.2%	Lung cancer deaths as % of total mortality.					
Findings for other sites not reported; skinfold thickness also associated.												
Cochrane ¹⁵¹ 1983	847 males, ages 55—64; 46 deaths	S Mortality	No significant difference in mean S between those developing lung cancer vs. others (168.0 vs. 168.9 cm).									
<i>Breast</i>												
de Waard ¹⁵² 1974	7,259 females ages 55—75; 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.									
Waalder ¹⁵³ 1983	17,361 females ages 46—85; 2,759 deaths	S Mortality	Independent effects for BW and S; study implicates "largeness" more than obesity. Women dying from breast cancer were taller (by 0.5 cm) than the general population for 29 of the 40 years studied.									
Authors attribute small difference to social class differences.												
Willett ¹⁵⁴ 1985	121,964 females ages 30—55 570 cases	BW, BMI S Incidence	RR = 1.0, 0.9, 1.0, 0.9, and 1.0 (postmenopausal) and 1.0, 0.9, 0.9, 0.7, and 0.7 (premeno- pausal) for BMI quintiles. Excess incidence in lean premenopausal women limited to small, well-differentiated tumors suggesting diagnostic bias. BW similarly related.									
RR = 1.0, 1.3, 1.3, 1.4, and 1.3 for S.												
Swanson ¹⁵⁵ 1988	7,149 females ages 25—74 121 cases	BW, BMI S Incidence	RR = 1.0, 0.8, 0.8, and 1.0 for BW quartiles. RR = 1.0, 1.0, 0.7, and 1.0 for BMI (kg/m ^{1.5}). RR = 1.0, 1.4, 1.3, and 2.0 for S. Strong association for elbow breadth.									

Table 2 (continued)
Cohort Studies Relating Body Size to Adult Cancer*

First author/ ref./year	Study population	Factors studied	Findings							
Tornberg ¹⁵⁶ 1988	46,570 females ages 17-74 1,182 cases	BW, BMI S Incidence	RR increased by 8% for each 10 kg BW increment and 10% for each 5 cm of S. Slight inverse association for BMI among women <50 years old.							
<i>Prostate</i> Greenwald ¹⁵⁷ 1974	~18,000 college males; 268 deaths	BW, BMI S Mortality	No significant case-control differences in BW, BMI (ponderal index: S/BW ^{0.3}), S or somatotype.							
Snowdon ¹⁵⁸ 1984	6,763 males ages ≥40 99 deaths	RBW Mortality	RBW (%)	70-89	90-109	110-129	130-245			
			RR	1.6	1.0	1.2	2.4			
<i>Multiple Sites</i> Blitzer ¹⁵⁹ 1976	56,111 females ages 30+ and of varying obesity; 2,571 cases	BW, BMI S Prevalence	RR = 1.0 and 1.0 for current BMI (lb/in) cut at 2.44 (all cancer). RR = 1.0 and 1.2 for current BMI (endometrium). RR = 1.0 and 1.6 for teenage BMI (endometrium; no change for all cancer).							
Lew ¹⁶⁰ 1979	755,500 males and females, ages ≥30	RBW Mortality	SEE TABLE 3							
Williams ¹⁶¹ 1981	1,209 males and females, ages 30-62; 691 cases	RBW, S Incidence	Uterine corpus and breast cancer associated with increased S. No association for RBW and cancer.							
Nomura ¹⁶² 1983	8,000 males, ages 45-68; 646 cases	S Incidence	All cancer incidence rate 74.6, 71.4, 74.7, 83.0, and 88.0 per 1,000 for S 140-157 to 170-188 cm. Possible association for lung, prostate and other non-GI cancers.							
Waaler ¹⁶³ 1984	1.8 million males and females, ages 15-90	BMI, S Mortality	Stomach and lung cancer inversely related to BMI; colon positively associated. No cancer - S association. Few data presented.							
Whittemore ¹⁶⁴ 1985	10,115 males and females, college age; 2,031 cases	BW, BMI S Incidence	Renal and bladder cancer associated with increased BW (not BMI) in college. Breast cancer related to high BMI (not BW) in college. S and change in BMI after college not associated with cancer.							
Nomura ¹⁶⁵ 1985	8,006 Japanese males, ages 45-68 years; 646 cases	BMI Incidence	BMI quintile	(<21.3)	Q1	Q2	Q3	Q4	Q5	(>26.3)
			Stomach	26.4	15.8	10.3	4.2	12.3		
			Colon	12.2	11.6	15.7	12.9	17.4		
			Prostate	11.4	9.8	15.4	13.3	14.2		
			Stomach and lung cancer account for inverse association of total. Trend for colon cancer restricted to ages ≥55 and associated with BW gain since age 25.							
Albanes ¹⁶⁶ 1988	12,554 males and females, ages 25-74 859 cases	S Incidence	RR = 1.0, 1.5, 1.4, and 1.4 for S ≤169 to >178.6 cm (all sites, men). RR = 1.0, 1.8, 1.8, and 2.1 (colorectum, men) and 1.0, 1.4, 1.3, and 2.1 (breast, women). Association primarily in men and for leg length (vs. sitting height).							

Note: BW = body weight; BMI = body mass index (weight/height², unless otherwise specified); RBW = relative body weight; S = stature; and RR = relative risk.

However, represent the actual (or observed) cancer mortality compared to the total all-cause mortality rate of the cohort, within sex and weight groups. Since overweight individuals in these and some other cohort studies experienced greatly increased mortality from several other illnesses (particularly cardiovascular, renal and gastrointestinal diseases, and diabetes mellitus), the comparison of cancer mortality to total mortality in this manner could reduce the observable excess cancer deaths in the overweight categories. This is because, in theory, some overweight individuals who would have gone on to develop cancer later in life may have died earlier of other causes, while leaner individuals less prone to other illnesses would become overrepresented among the cancer cases. This may be especially relevant to the assessment of cancer mortality from the cardiovascular disease study cohorts which follow.

Several investigations of the relationship between cancer incidence or mortality and BW or mass have been conducted in the context of prospective cardiovascular disease studies. Comparing Framingham study data to the BBPS discussed previously, Sorlie et al.¹⁴⁴ demonstrated somewhat increased total cancer mortality among men in the lowest relative BW category during the initial six years of follow-up. Similarly, Wallace et al.¹⁴⁵ evidenced lower BMI in men and women who later developed cancer (compared to non-cancer controls). However, the association was significant only among those ≤ 59 years old at the time of study entry, for "smoking-related" cancers, and malignancies occurring more than 2 years after study entry. Using data available from the Whitehall Study, Jarrett et al.¹⁴⁶ showed that increased total cancer mortality in the lowest BMI quintile and an overall inverse association were

due to underweight cases diagnosed primarily within 2 years of study entry. The BMI-cancer mortality relation beyond 2 years of follow-up was J-shaped, with increased cancer beginning with the second lowest quintile. Avons et al.¹⁴⁷ also demonstrated that men in the lowest quintile of prospective study exam BMI 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 are very similar to the findings of Rhoads and Kagan, who observed that increased cancer mortality among the leanest men at examination was explained by those who had lost weight since age 25, while the leanest at age 25 experienced the lowest cancer rate.¹⁴⁸

Eight prospective investigations of single cancer sites have been published. Phillips et al.¹⁴⁹ found the colorectal cancer mortality rate to increase with RBW above ideal weight. Lean men and women also experienced higher rates, however. In a study of mortality among men from the West of Scotland, Garn et al.¹⁵⁰ using various measures of body fatness (including skinfold thickness and radiographic fat shadows) noted increased lung cancer mortality among the leanest men compared to those most obese, men who instead experienced greatly increased cardiovascular disease mortality. De Waard and Baanders-van Halewijn showed that BW (and to a lesser degree, BMI) was positively associated with postmenopausal breast cancer incidence.¹⁵² These results were corroborated by a later study of pre- and postmenopausal women by Tornberg et al.¹⁵⁶ In contrast, Willett and coworkers did not find a relationship between postmenopausal breast cancer and BMI, but did demonstrate an inverse relation among premenopausal women.¹⁵⁴ This observation was attributed by the authors, in part, to easier and earlier diagnoses of breast masses among lean women. Swanson et al.¹⁵⁵ also demonstrated no association for BMI or weight, although risk increased with peripheral body fat, as assessed by triceps skinfold thickness. Finally, weight, ponderal index, or somatotype were no different for men who developed prostate cancer and those who did not in the study by Greenwald et al.,¹⁵⁷ in contrast to Snowdon et al.¹⁵⁸ who evidenced increased prostate cancer mortality among overweight men (relative risk = 2.5 for men \geq 130% RBW vs. men 90 to 109% RBW). Similar findings for obesity and breast cancer were mentioned in the latter study, but these data were not presented.

Several cohort studies examined multiple cancer sites at follow-up. Blitzer et al. showed no relationship between the degree of obesity and cancer among 56,000 obese women.¹⁵⁹ Only endometrial cancer was associated with obesity, particularly teenage obesity. Cancer of the uterine corpus was also related to obesity in a report concerning the Framingham cohort by Williams et al.,¹⁶¹ while in the study conducted by Whittemore and colleagues, subsequent breast, kidney, and bladder cancers were related to increased weight during college.¹⁶⁴ Nomura et al.¹⁶² demonstrated that BMI at entry was positively

associated with risk of colon and prostate cancer, and negatively associated with stomach and lung cancer in a follow-up to their previous report examining total cancer mortality. The association for colon cancer was seen among those \geq 55 years old at the time of examination, and those who gained weight after age 25, while a stronger positive association for prostate cancer was evident for BMI at age 25. Weight loss after 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 meaningful site-specific differences being overlooked in analyses of total incidence or mortality. Waaler reported a similar disparity between sites, with colon (positively) and stomach and lung cancers (inversely) related to BMI.¹⁶³

Between 1959 and 1972 the American Cancer Society conducted a prospective study of 750,000 men and women in the U.S.¹⁶⁰ In this study, total mortality, expressed as ratios of rates between weight groups, 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 3. Total cancer mortality was higher among those overweight (i.e., $>$ 110% of average) when compared to those 90 to 109% of average weight. For men, this relation was statistically significant for cancer of the colon, rectum, and prostate, while in women, cancer of the breast, uterus (cervix and endometrium), gallbladder, and ovary were most increased among those overweight. Persons in the underweight categories in general experienced reduced cancer mortality compared to 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, all cancers that are associated with cigarette smoking.

In summary, the cohort studies reviewed provide more equivocal evidence regarding BW as compared to the case-control investigations. Of the cohort studies, one third support a positive cancer - BMI (or obesity) relation for breast, large bowel, prostate, or multiple-site cancer. Another third demonstrates either no association or gives mixed results; for example, higher total cancer rates for very lean and very obese persons (the BS¹⁴³), or findings which differ by cancer site, as in the study by Nomura et al.,¹⁶² which show a positive colon cancer-obesity association and an opposite trend for lung cancer. In the remaining studies of BMI, which primarily involve men, leanness as defined by a low BMI score has been associated with higher rates of cancer, specifically lung, bladder, stomach, and total cancer incidence and mortality. Confounding by cigarette smoking, which is related both to adult leanness and lung and other cancers, has been suggested as one explanation for the latter conflicting reports, most of which did not consider and adjust for cigarette use.^{169,170} One measure of this effect is available from the American Cancer Society study

Table 3
Cancer Mortality Ratios* According to Relative Body Weight and Cancer Site

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
Colorectum	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	M		0.81	1.00	0.90	1.19		
	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	
	F	0.92	0.99	1.00	1.04	0.85		

* 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). Data from Lew and Garfinkel.¹⁶⁰

which revealed that the excess cancer among lean individuals was confined to smokers, particularly smokers of 20 or more cigarettes daily (see Figure 1). (The average age-adjusted cancer mortality for all smoking categories combined serves as the reference, i.e., mortality ratio = 1.0.) By contrast, a nearly linear trend between RBW and total cancer mortality was observed for both men and women among nonsmokers, demonstrating that leanness in the absence of exposure to cigarettes was protective against cancer. A similar "bias" has been observed concerning BMI and overall mortality.¹⁷¹ The finding in several studies that weight loss after age 20 or 25 is associated with increased cancer (e.g., lung) mortality later in life is also consistent with the effect of lifetime cigarette smoking on both BW and cancer risk. Since smoking-related cancer mortality is greater in men than in women, such a confounding effect could also explain the apparent sex difference with regard to leanness and increased cancer mortality. Furthermore, the observed positive findings for lung cancer and stature⁷² (see the following), an anthropometric factor which cannot readily be affected by adult smoking, offer indirect evidence that smoking may be biasing the previously mentioned studies of BW.

Another factor mentioned that may account for leanness and weight loss among persons later developing cancer is the effect of antecedent, subclinical illness on BW and body fat. Screening individuals for major diseases prior to study entry as was done in some of the previously mentioned cohort studies would reduce such a bias. Other investigations have 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).^{144,146,162} Only one smaller study observed the opposite trend.¹⁴⁵ Failure to demonstrate increased

Cancer Mortality Ratio According to Relative Body Weight by Sex and Smoking Status

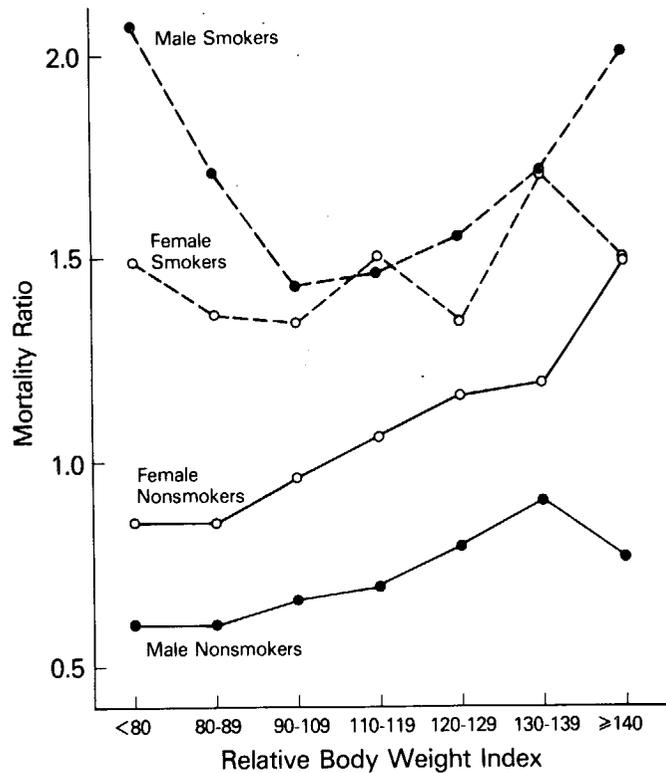


FIGURE 1. The differing relationship between cancer mortality and relative body weight among non-smokers and current smokers of 20+ cigarettes per day. Up to 12 years of follow-up for over 750,000 men and women from the American Cancer Society study data of Lew and Garfinkel.¹⁶⁰

leanness among cases in most of the case-control studies discussed is difficult to reconcile with such an effect for subclinical illness, however, since cases for these investigations are usually obtained, and body size is determined, at or around the time of diagnosis when greater disease-related weight loss might be observed. This inconsistency would suggest either site-specific differences in the expression of this effect (i.e., lung and gastric greater than breast and renal cancer), underestimated relative risks in the case-control studies, or the potential for some study recruitment bias (e.g., obese persons could be less willing than others to participate as controls).

B. Stature and Cancer

Altogether, in approximately 50 studies (including 4 ecologic analyses cited previously for their findings concerning BW⁶⁴⁻⁶⁷) the relationship between S and adult cancer has been evaluated (see Tables 1 and 2). In most of these instances, absolute or relative body weight was also investigated. Over half of the studies demonstrated a positive relationship between S and cancer, while the others generally reported no association. Breast, endometrial, colorectal, and lung are cancers for which the majority of investigations demonstrated increased risk among taller persons. The importance of absolute as opposed to relative body weight is emphasized by these observations concerning increased cancer risk among taller men and women. For only one site (prostate) did most investigations show no association for S. While the majority of studies examining BW and S demonstrated positive associations with cancer for both factors, a few did so only for weight (breast, prostate, ovary, and choriocarcinoma) or only for S (breast). S in relation to childhood cancers has been reported in six studies (see the following).

C. Body Size and Childhood Cancers

There are 16 published investigations of the relationship between body size and childhood cancers (see Table 4). These include 11 studies of birthweight,^{172,174-177,179,180,183-185,187} 2 studies of childhood weight and S,^{173,181} and 3 studies of childhood S alone.^{178,182,186} (Three studies of testicular cancer in young men are included in Table 4 because they involve birthweight.^{179,183,184}) Birthweight is a function of several factors including gestational age, sex, parity, ethnicity, and maternal size, nutrition, disease, and smoking habits.¹⁸⁸ Birthweight is also proportional to the number and size of cells in the neonate. Six of the studies demonstrated higher cancer risk for increased birthweight,^{172,174-176,180,185} three showed no association,^{177,184,187} one an inverse relationship,¹⁷⁹ and one demonstrated increased risk for high and low birthweight infants.¹⁸³ Hematopoietic and central nervous system tumors predominate among the positive studies of birthweight.

With regard to S in childhood, cases were taller (and in one study, heavier¹⁷³) than controls in two studies (bone, leukemia),^{173,178} while in other investigations of Ewing's sarcoma¹⁸¹ and leukemia,¹⁸² there were no such consistent differences.

Finally, one study gave mixed results, with only female Hodgkin's or non-Hodgkin's lymphoma cases being taller than controls.¹⁸⁶ (Another positive study of S and Hodgkin's disease¹³³ failed to provide the patient age range and was included in the previous section concerning adult body size and Table 1.) These investigations of childhood cancers offer some data supportive of a role for not only adult S but also S during growth. The fact that birthweight may influence the subsequent occurrence of childhood malignancies provides further evidence for the role of absolute body size, since higher birthweight newborns are known to become children and adults of above average size.

IV. BODY SIZE AND CANCER SURVIVAL

Most of the preceding studies show that the risk of developing cancer increases with body size. In addition, some demonstrated higher cancer mortality rates among overweight persons compared to those at or near "ideal" BW. With regard to body size and cancer survival, several investigations demonstrate the prognostic significance of body size in malignancy. Reduced breast cancer survival (5 to 15 years) and higher recurrence rates have been demonstrated for pre- and postmenopausal patients of greater absolute BW in all clinical investigations of body size¹⁸⁹⁻¹⁹⁴ but one.¹⁹⁵ With the exception of three studies,¹⁹⁶⁻¹⁹⁸ survival was also inversely related to BMI (or fatness),^{192,193,199-202} and overweight and tallness have been associated with higher incidence of multiple primaries in one investigation of breast cancer.²⁰³ In most of the reports, BW was related to survival within each disease stage, although some demonstrated a stronger negative association with survival in earlier stages. BW and fatness are, therefore, predictors of breast cancer survival independent of other prognostic factors which should be taken into account when designing and analyzing results from clinical therapeutic trials. There is little evidence that S affects outcome, however.^{192,195}

In contrast to this fairly uniform picture for survival and weight, there appears to be less agreement as to whether large tumor size, positive nodes, advanced stage disease, or positive estrogen receptor status are associated with obesity among women with breast cancer.²⁰⁵⁻²¹¹ Several studies found that overweight patients presented with more advanced disease, but as already mentioned, this association was not responsible for the weight-survival relationship. Howson et al.²⁰⁸ summarized the investigations of weight, obesity, stage, and estrogen receptor status and, consistent with their findings, saw insufficient evidence for an association between body size and the prognostic factors. While this issue remains to be resolved in future studies, more advanced disease among overweight breast cancer patients does not appear to explain their survival disadvantage.

Some early researchers in this area attributed their observations to the tumor-promoting effects of enhanced estrogen

Table 4
Birthweight, Childhood Stature and Weight, and Childhood Cancers

First author/ ref./year	No. of cases/site	Factor(s) studied/ ages	Findings
MacMahon ¹⁷² 1962	4198 Multiple	Birthweight 0—11 years	Children diagnosed with cancer of the brain or kidney, leukemia, lymphoma, or other cancers had slightly higher birthweight. Regional record study of mortality; birth to 11 years.
Fraumeni ¹⁷³ 1967	167 Bone	BW, S 0—18 years	Cases taller than general population and "controls" (cases of non-osseous cancer). Similar (but weaker) association for BW (incidence). Association stronger for osteogenic sarcoma than for Ewing's sarcoma.
Fasal ¹⁷⁴ 1967	802 Leukemia	Birthweight 0—9 years	RR = 1.0 and 1.2 for birthweight (cut at 9 lb); males. RR = 1.0 and 2.1 for birthweight (cut at 8.5 lb); females. Adjusted for maternal age and social class.
Wertelecki ¹⁷⁵ 1973	72 Leukemia	Birthweight <15 years	Cases heavier at birth than their sibling controls, even after controlling for sex, birth order, and maternal age.
Gold ¹⁷⁶ 1979	84 Brain	Birthweight 0—19 years	RR = 2.6 for birthweight \geq 8 lb. Increased risk similar for other malignancies (data not shown).
Grufferman ¹⁷⁷ 1982	33 Rhabdomyosarcoma	Birthweight 0—14 years	RR = 0.9 for birthweight >3.4 kg. RR = 0.6 for birthlength >50 cm.
Broomhall ¹⁷⁸ 1983	236 Leukemia	S 0—12 years	Cases significantly taller than general population.
Depue ¹⁷⁹ 1983	108 Testis	Birthweight 16—30 years	RR = 3.2 for birthweight <6 lb.
Daling ¹⁸⁰ 1984	681 Multiple	Birthweight 0—15 years	Increased birthweight (>4000 g) among cases, especially in 0—2 year olds. Association stronger in females.
Pendergrass ¹⁸¹ 1984	291 Ewing's sarcoma	BW, S 2—18 years	Male cases somewhat heavier than population mean. Female cases shorter and lighter. Only cases over 150 cm were taller than peers. No BW or S effect on survival.
Bessho ¹⁸² 1986	44 Leukemia	S Age not given	No case control difference in S.
Brown ¹⁸³ 1986	202 Testis	Birthweight 18—42 years	RR = 13.5, 1.2, 0.9, 1.0, 1.2, and 1.5 for birthweight \leq 5 to >9.0 lbs (reference group 7—8 lb).
Malone ¹⁸⁴ 1986	145 Testis	Birthweight 10—34 years	No association for birthweight or length and cancer.
Eisenberg ¹⁸⁵ 1987	3868 Multiple	Birthweight 0—14 years	No consistent associations for leukemia, solid tumors or other RES neoplasms. Female solid tumor cases ages 1—10 had higher birthweight. Male solid tumor cases 0—2 had lower birthweight.
Pui ¹⁸⁶ 1987	3657 Multiple	S 0—18 years	No case control difference in S except for taller Hodgkin's and non-Hodgkin's lymphoma cases (girls) and acute lymphocytic leukemia cases.
Shu ¹⁸⁷ 1988	309 Leukemia	Birthweight 0—14 years	RR = 1.0, 1.1, and 1.7 for birthweight \leq 3000 to \geq 3500 g.

Note: BW = body weight; S = stature and RR = relative risk.

production in adipose tissue.^{189,190,201,211} Poorer survival among obese premenopausal women, however, suggests that alternative mechanisms are involved, since extra-gonadal estrogen sources would probably be of lesser importance in this group.

Abnormalities of other trophic hormones or sex-hormone binding globulin levels which occur among obese women have also been proposed as possible mechanisms.²¹²⁻²¹⁴ Alternatively, diminished immunological status or nutritional effects (e.g., higher fat and cholesterol intake)^{189,197} have been suggested as reasons for the decreased survival of overweight women with cancer.

V. POSSIBLE MECHANISMS

Animal experiments corroborate most of the above observations concerning humans, and have been unique in their

ability to elucidate several specific aspects of the relationships involved. For example, animals exposed to exogenous thyroxin, low environmental temperature, or high levels of physical activity, all of which resulted in lower BW despite increased energy intake, experienced reduced tumor incidence.^{44,45,215,216} Efficiency of BW gain throughout life is associated with increased tumor incidence.²¹⁷ These studies, as well as others identifying the importance of "net energy,"^{218,219} highlight the crucial role played by energy balance per se in tumorigenesis. Also, experiments which have examined body composition demonstrate that calorie restricted groups experience reductions in both lean and fat tissue mass,^{44,219} suggesting that the observed inhibitory influence of negative energy balance on carcinogenesis may be partially due to effects on growth, in accord with the human data regarding stature (childhood and adult) and absolute BW. Finally, energy restriction inhibits tumori-

genesis even when applied during presumably late stages of carcinogenesis, i.e., following exposure to a one-step or "complete" carcinogen (rather than prior to or during such exposure),^{220,221} or among older animals fed *ad libitum* up to approximately "middle-age" but restricted thereafter.^{4,222} Thus, although reduced caloric intake throughout life may be the most effective intervention, there is some evidence for efficacy when energy restriction is instituted at older ages and after carcinogenic exposures. This has important implications for anti-carcinogenesis in humans since the majority of cancers occur later in life and effects on promotion may be most relevant and useful for prevention. These experimental data point out the need for more complete information concerning energy balance, energy balance changes over time, and body composition in future investigations, particularly in humans.

Given our current knowledge, the potential mechanisms whereby energy balance or body size affect carcinogenesis can only be speculated upon. Energy balance is known to influence a large number of physiological functions including body temperature, basal metabolic rate, protein synthesis, the activity of several enzymes, cell-mediated immunity, and endocrine status (i.e., levels of pituitary hormones, insulin, T₃ and T₄, and estrogens).²²³⁻²²⁹ In addition, DNA synthesis and cell division are positively related to energy balance.²³⁰⁻²³² A role in human malignancy has been suggested for some of these factors,^{228,229,233} which represent mechanisms generalizable to multiple sites (e.g., cell number and the rate of cell division²³³) or which are site-specific.

For example, hormonal mechanisms have received the greatest attention with respect to adenocarcinoma of the breast, probably the most widely studied cancer from an etiologic and epidemiologic standpoint. It has long been hypothesized by many that enhanced estrogen production in overweight and obese women accounts for their increased risk of developing breast cancer after the menopause.^{234,235} (Alterations in sex-hormone binding globulin and non-protein-bound estrogen levels, specifically, have also been implicated.^{213,214}) As formulated most recently by de Waard and Trichopoulos,²³⁶ estrogenic stimulation of breast ductal epithelium is thought to in some way lead to greater cell division and exposure of cells malignantly transformed earlier in life. Premenopausal women may not be vulnerable to the breast cancer risk enhancement of obesity for one or more reasons including (1) before the menopause, ovarian estrogens are generally high and may overshadow the etiological importance of extra-gonadal (i.e., adipose tissue) sources; (2) premenopausal obesity is frequently associated with anovulation; (3) earlier detection of breast lumps (particularly smaller tumors) in lean, premenopausal women;¹⁵⁴ or (4) residual confounding by stature, which can be inversely related to some BMIs.⁵⁷ Body size is also related to age at menarche (inversely) and menopause (directly), offering other possible links to cancer.²³⁷ While these hypotheses have been discussed particularly with respect to breast cancer, they may

apply as well to endometrial and ovarian malignancies which are also strongly associated with body size and considered to be hormonally related.

Colon cancer has been linked to greater energy intake and body size, and to lower levels of physical activity, and several mechanisms have been suggested to explain those observations. Local effects of greater food intake could involve increased exposure of the colonic mucosa to exogenous carcinogens or bile acids, or to increased carcinogen activation in the bowel lumen.²³⁸ Greater rates of mucosal epithelium proliferation in response to increased food intake are also possible.^{238,239} Alternatively, longer intestinal transit time due to dietary differences²⁴⁰ or physical inactivity⁴⁸ have been suggested. Further research is needed to test these and other hypotheses of site-specific mechanisms.

More general mechanisms have also been forwarded to explain the relationships described in this review. Various and often complex changes in the immune system during periods of calorie restriction have been reported, such as enhanced T-cell mitogen response or natural killer cell activity, and linked with reduced experimental tumor rates.^{228,241} Alternatively, the production of free radicals, which may be related to carcinogenesis,²⁴² is probably influenced by energy balance or metabolism. We recently postulated that energy balance and body size affect carcinogenesis through their influence on the total number of proliferating cells.²³³ According to this hypothesis, increasing either the rate of cell division within the tissue or the absolute number of cells, particularly stem cells, through enhanced growth could lead to greater risk of a malignant transformation. The theory accounts for both the effects of energy balance and overweight on cell proliferation in adults and for the observations concerning S and cancer since taller persons may have larger organs (e.g., colon²⁴³).

VI. CONCLUSIONS

Future research in this area should further test whether energy balance and body size are causally related to human carcinogenesis, and address some of the contradictions and inconsistencies raised in previous investigations. Measures should be taken to minimize sources of error, some of which are common in human observational studies, including differences in subject selection, other carcinogenic exposures (e.g., cigarette smoking), and disease stage, as well as imprecise measurement of "exposure" — that is, energy balance and body size. Focusing on major cancer sites which have been less well studied, such as lung, prostate, or pancreas, would extend our current knowledge, as would active exploration of potential mechanisms about which we know relatively little. Prospective or cohort studies will generally be most useful for less biased (with respect to disease onset) appraisal of intake, activity and weight, assessment of weight change over time, and both site-specific and total cancer incidence. The collection

of all relevant data, including energy intake and expenditure, anthropometry (including weight changes over time and body composition), and parameters related to mechanisms of action, will permit a more complete assessment of the involved factors and help elucidate their interaction. Attention should be given to the evaluation of multiple (i.e., early and late) periods of "exposure" and not necessarily only those most readily available. For example, although body size at the time of cancer diagnosis has been more commonly investigated in case-control studies, height and weight during childhood, adolescence, and young adulthood are predictors of cancer risk which should also be measured or queried. In this regard, the identification and utilization of appropriate historical information such as military recruit or school medical records may offer unique (and less costly) analytical opportunities. Similarly, the relationship between birthweight and adult cancers should be delineated. Laboratory research, including both animal experimentation and human studies, is needed to complement epidemiological investigations and test the various mechanisms which have been previously put forward or that will be suggested in the future.

The importance of energy balance and body size in determining susceptibility to malignancy has generally been underestimated until recently. In addition to some of the potential research outlined previously, our current knowledge may justify various levels of application in appropriate human populations. Reducing the prevalence of overweight and obesity in children and adults, a generally healthful goal from the standpoint of not only other important causes of morbidity such as coronary heart disease,²⁴⁴ but of human lifespan,²⁴⁵ would likely also decrease cancer rates and improve survival (e.g., in breast cancer). Although compliance with weight reduction regimens among adults has been relatively poor historically, efforts aimed at targeting high-risk populations, multiple factor designs, and multidisciplinary approaches may make intervention studies of BW and cancer more feasible.

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