The use and interpretation of anthropometric measures in cancer epidemiology: A perspective from the World Cancer Research Fund International Continuous Update Project

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ABSTRACT

Anthropometric measures relating to body size, weight and composition are increasingly being associated with cancer risk and progression. Whilst practical in epidemiologic research, where population-level associations with disease are revealed, it is important to be aware that such measures are imperfect markers of the internal physiological processes that are the actual correlates of cancer development. Body mass index (BMI), the most commonly used marker for adiposity, may mask differences between lean and adipose tissue, or fat distribution, which varies across individuals, ethnicities, and stage in the lifespan. Other measures, such as weight gain in adulthood, waist circumference and waist-to-hip ratio, contribute information on adipose tissue distribution and insulin sensitivity. Single anthropometric measures do not capture maturational events, including the presence of critical windows of susceptibility (i.e. age of menarche and menopause), which presents a challenge in epidemiologic work. Integration of experimental research on underlying dynamic genetic, hormonal and other non-nutritional mechanisms is necessary for a confident conclusion of the overall evidence in cancer development and progression. This article discusses the challenges confronted in evaluating and interpreting the current evidence linking anthropometric factors and cancer risk as a basis for issuing recommendations for cancer prevention.

INTRODUCTION

Since the early 1980s, evidence has accumulated from a rapidly growing body of epidemiologic studies (1, 2) showing an association between increased adiposity and the risk and progression of cancer. This association is supported by clinical studies (3, 4), which together with a better understanding of the biology of cancer (5) have helped to identify mechanisms through which energy balance might influence the cancer process. Together, this evidence supports a causal association between increased adiposity and cancer occurrence (1, 2, 6).

Anthropometric measures reflecting body size and composition have been associated with site-specific cancer development (1), with growing evidence that body composition plays important role in cancer treatment, side effects and survival (7). These measures include height, weight and waist and hip circumference, and derived indices such as BMI, waist-to-hip ratio and waist-to-height ratio. Measures of birth size and weight, growth during childhood (sometimes linked with measures of maturation such as age at menarche or menopause), and/or change in weight in adulthood have also been considered if available. However, the precise relationships between these variables are often poorly characterised (8). Furthermore, these measures are subject to additional limitations in that they mask the processes underlying observed associations, such as developmental factors that may give rise to critical periods of susceptibility where intervention would be most beneficial. Measures that do not distinguish lean from adipose tissue may also obscure any separate roles of low lean mass and high adiposity in determining cancer risk. Consequently, it is important to be aware of the advantages and limitations of using anthropometry to unravel precise causal connections between nutritional state and cancer, particularly when using these to make clinical and public health recommendations.

In this paper, we draw on the experience from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Second Expert Report *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (1) and the Continuous Update Project (2), in which systematic reviews and meta-analyses are conducted on the links between nutritional exposures, anthropometric measures, and cancer risk. An independent expert panel then judges the strength of the evidence based on the likely causality of associations using a priori criteria (see supplementary information), as a basis for making recommendations for cancer prevention. The purpose of this article is to discuss key methodological challenges and issues in assessing and interpreting the evidence on anthropometric measures and cancer risk.

ANTHROPOMETRIC FACTORS AND CANCER: ASSESSING THE EVIDENCE

The role of epidemiologic studies

The Continuous Update Project (2) has identified strong evidence for links between adiposity, adult weight gain, height, and several cancer types (see Table 1), based on a comprehensive review of the current epidemiologic literature and a-priori causality criteria (1) (see supplementary information). Epidemiologic investigations are critical in understanding how anthropometric and other factors relate to site-specific cancer risk and prognosis. They represent the best available method for establishing population-wide associations in free-living individuals. Assessing the overall body of evidence, however, requires the evaluation of studies that provide mechanistic insights, including *in vitro* investigations, animal studies, and human experimental studies on intermediate factors (for example, hormonal, metabolic, immunological, and epigenetic responses). These mechanistic studies are important for ascribing causality to observed associations, and laboratory studies permit hypothesis-testing under controlled conditions to a greater degree than is feasible in free-living human populations. However, caution must be exercised as findings from

animal models and cell lines may not be directly generalisable to humans; in particular, the identification of susceptible individuals can only be determined in humans. As randomised interventions on body size and composition and cancer risk are difficult, the current inference of causal relationships depends on a synthesis of evidence from human epidemiologic, metabolic, animal, and mechanistic studies.

[Table 1 about here]

Key challenges in evaluating the impact of adiposity on cancer risk

Studies related to adiposity represent a unique challenge in epidemiology. Most epidemiologic studies have used anthropometric measures such as BMI, weight change over a specified time, and body circumference measures as markers of body composition. Although such markers are imperfect, and may reflect genetic and other non-nutritional factors, at a population level markers of adiposity (e.g., higher BMI or waist circumference) are strongly correlated with systemic and tissue factors that may potentially influence cancer, such as systemic low-grade inflammation, oestrogen levels in postmenopausal women, insulin resistance and hyperinsulinemia (9).

Adipose tissue in humans is a structural and thermal buffer, a store of energy in the form of lipid (principally triglycerides), and an active endocrine organ involved in hormonal secretion and metabolism that contributes to appetite regulation, immune function and inflammation (10, 11). Abdominal visceral adipocytes are more metabolically active than abdominal subcutaneous adipocytes, as they have high lipolytic activity and release large amounts of free fatty acids (12, 13). Some studies have shown that for certain cancers, abdominal obesity may be associated with risk for cancer independent of overall obesity (e.g. (14)). Therefore, ideal measurements

of adiposity include the regional distribution and site of deposition of the adipose tissue, including that within and around specific organs.

Evidence based on associations between anthropometric measures such as BMI and cancer is taken to represent adiposity, reflecting its interpretation in the biological context of a wider body of evidence. High BMI itself is not a cause of cancer. It is interpreted as a marker, which, supported by a body of mechanistic evidence that biological factors related to adiposity can influence the risk of development or progression of cancer, is judged to be the causal exposure. Equally, it is uncertain whether waist circumference, or waist-to-hip ratio, should be interpreted as markers of visceral adipose tissue specifically, or of abdominal subcutaneous adipose tissue, or simply of total body fat. As with BMI, the circumference itself is obviously not the causal factor, but uncertainty exists in its interpretation as a marker of the internal metabolic milieu that underpins the association.

Similarly, adult attained height consistently predicts increased risk of several cancers (15), although clearly height is not the causal factor *per se*. Height acts as a marker for the complex interplay of genetic, nutritional and other environmental factors that determine the growth trajectory and culminate in final height. It must also be noted that adult height does not fully characterize the growth trajectory (either in terms of height or body composition). For instance, the timing of the BMI rebound in childhood (referred to as the 'adiposity rebound' (16)) during growth has been linked to susceptibility for other chronic conditions including subsequent obesity, metabolic syndrome, diabetes and cardiovascular disease (17, 18). It is uncertain whether there is also a link between adiposity during growth and cancer. This may be an important avenue for exploration, given that known associations between birth weight and adult height operate in different directions for cardiovascular disease and cancer (19, 20).

In addition to issues of interpretation of anthropometric measurements as indicators of body composition in relation to cancer risk, observational evidence also needs to take account of potential confounders or effect modifiers such as smoking, alcohol intake and hormone use, as well as intermediate factors such as physical activity and specific dietary factors.

Limitations of current anthropometric measurements

Body Mass Index (BMI), defined as the quotient between weight in kilograms and height in meters squared (kg/m^2), is the most commonly used marker of adiposity in epidemiologic studies due to simplicity of assessment, low costs and high precision and accuracy. Definitions for classifying and reporting population-level healthy weight, overweight and obesity have historically been based on anthropometric measures. Overweight and obesity are conventionally defined in relation to BMI in excess of 25 and 30 kg/m^2, respectively (21) in most populations, with lower cutpoints for Asians (22, 23).

Although BMI represents a useful indicator of adiposity, it is an imperfect measure of body composition, because it does not differentiate between lean and adipose tissue mass; the relative proportions of which vary between individuals, and with age, sex, and race/ethnicity (24, 25). In addition, BMI provides no information on the distribution of adipose tissue, whether central (in the abdomen, including the abdominal wall and viscera), peripheral (in the buttocks and extremities), or in the organ at risk. BMI is also less reliable as an indicator of adiposity among older people, due to reduction in height, loss of muscle (lean tissue) and increase in adipose tissue that occurs with aging, particularly after menopause in women (26). Thus, BMI shows a stronger (positive) correlation with estimates of adipose tissue in younger individuals, but shows a stronger (inverse) correlation with muscle tissue in older individuals (27).

Epidemiologic studies often rely on self-reported height and weight which may include systematic errors in calculations of BMI; people tend to under-report weight and over-report height (28). However, studies have shown a strong correlation (>0.9) between self-reported and measured weight and height (29-32). Furthermore, the impact of such systematic measurement error on relative risk estimates in epidemiologic studies is generally small (33). BMI cut-offs are therefore useful at the population level, but may not accurately reflect adiposity of individuals.

Furthermore, comparison across studies examining cancer risk according to BMI is problematic if studies have assessed risk across specified quantiles. As the distribution of BMI varies between populations, at different stages of life and different time periods, the specific groupings may not be comparable. Other studies report risk according to WHO BMI categories, which may mask associations within these categories.

Measures of adipose distribution typically include waist and hip circumferences, waist-to-hip ratio and waist-to-height ratio. Waist and hip circumference measurements show greater inter-observer variability than assessments of weight or height. This is in part attributed to the lack of a standardised methodology for measuring waist and hip circumference (21). However, these measures are useful to identify abdominal obesity, commonly defined as a waist-hip ratio of ≥0.90 for males and ≥0.85 for females, with waist measurement cut-offs varying according to sex and ethnicity (21). However these measures cannot differentiate between visceral and subcutaneous adipose compartments (34). Visceral adiposity is positively related to cardiovascular disease, metabolic syndrome, type 2 diabetes, and several types of cancer (35-37), whereas subcutaneous adipose tissue has an anti-atherogenic effect (13). The associations of these different adipose tissue compartments are less well

characterised in assessment of cancer risk, at least partly because circumference measures and ratios used may be more variable between populations, and their interpretation is less studied and not well established. (38).

Weight change. The association of weight gain and loss with cancer risk has been evaluated in many studies and presents additional challenges.

Weight gain throughout adulthood has been shown in the literature to increase risk of several cancers, such as postmenopausal breast cancer, endometrial, ovarian cancer, colon cancer, prostate cancer and kidney cancer (39, 40). The Continuous Update Project has confirmed this link in endometrial, pancreatic and postmenopausal breast cancers (see Table 1). Weight gain may be a better marker of adiposity than BMI because it represents a snapshot of the weight trajectory throughout adult life, which in most adults results in accumulation of adipose tissue (39). However, the assessment of weight gain in most studies has been based on recall, which may have led to measurement error, but generally expected to be random and resulting in attenuation of effect estimates (39).

Intentional weight loss has been associated with reduced risk of cancer (41, 42), providing further support for a link between excess adiposity and disease risk. This type of evidence has been challenged, however, (43) meaning that caution must be exercised when interpreting data on weight in isolation. Furthermore, information on the intervention for weight loss is not always clearly reported, additionally clouding the findings. Notably, intentionality of weight loss cannot always be included alongside measurements. The possibility of “reverse causation”, resulting from undiagnosed pre-clinical disease or other chronic illness leading to weight loss, may produce spurious findings. One way to avoid this bias is to exclude subjects with serious illness and weight loss during the first few years of follow-up (44). However,

even after excluding these participants, the possibility of undiagnosed illness remains, particularly in certain populations such as smokers. Bias due to reverse causation may also occur when illness or associated treatments cause weight gain (45). Overall, there is no clear solution in addressing the potential impact of reverse causation in studies exploring the relationship of BMI and cancer. Nevertheless, bariatric surgery for weight loss has been associated with reduced risk of adiposity-related cancers (42), providing additional support for the obesity-cancer link.

Measures of adiposity include skinfold thickness, which can be used to predict adipose tissue and its distribution; however the estimate is prone to measurement error and generally unfeasible to use in large population based studies. Bioelectrical impedance analysis is another method used to measure adiposity that estimates lean and fat mass based on the principle that resistance to an electric current is greater in adipose tissue than in lean tissue. However, bioelectrical impedance measures yield similar estimates of disease risk to those derived from BMI alone (46).

More direct and sophisticated measures of adiposity are available, such as air displacement plethysmography, underwater weighing (hydrodensitometry), dual-energy X-ray absorptiometry, ultrasound, computed tomography and magnetic resonance imaging (47). These methods show excellent reproducibility and validity (48, 49) and are increasingly being employed to measure adiposity at the tissue or organ levels, particularly in small-scale studies that require a high level of accuracy. However, due to high costs and lack of portability, their use in large-scale epidemiologic studies has been limited.

Adult attained height represents a complex variable that depends on a combination of genetic, nutritional and other environmental factors. Greater height is associated with increased risk of many types of cancer, such as colorectal, ovarian and breast

cancer (1) (see Table 1). Hyperinsulinemia and enhanced levels of growth hormone and insulin-like growth factor 1, associated with maximal attained growth in pre-adulthood, may partly contribute to this relationship (50). However, adult attained height does not characterise the growth trajectory, and may also be determined in part by other aspects of maturation, including genetic factors that may also be associated with increased cancer risk.

Anthropometry throughout the life-course

Pre-adult energy balance is an important, though not sole, determinant of adult height and physiologic indicators such as age at menarche (51, 52). Both epidemiologic and mechanistic studies conducted at the whole body, cellular and molecular levels suggest that accelerated growth in terms of weight, height or the timing of maturation of various hormonally mediated processes (adrenarche, menarche, puberty, pregnancy, lactation and menopause) can modulate site specific cancer risk (1).

Birth weight, size and later growth (which can be assessed relative to established norms or standards) are predictors of risk for some types of cancer, such as colorectal, ovarian and breast cancer (1). An underlying susceptibility to cancer marked by excessive growth in utero and high birth weight (>4000g; macrosomia) (53), or impaired early growth marked by low birth weight (<2500g), may be revealed or activated by subsequent events later in life (54). These effects may in part be mediated by epigenetic control of gene expression, characterised by differential DNA methylation or acetylation of histones that define which specific genes are translated to bioactive proteins (55). Specific growth factors controlling adipose tissue growth and distribution may be affected, as well as hormonal responses including appetite control, thus defining subsequent obesity and disease risk, e.g. of diabetes (56).

Maternal obesity and gestational diabetes lead to excess fetal growth and excess adipose tissue at birth (57). Infants born with macrosomia are also at higher risk of obesity in later life, have earlier pubertal maturation and an increase in abdominal obesity, and increased risk of breast cancer (58). Recent evidence supports the notion of differential epigenetic changes in offspring of obese fathers and mothers, depending on which parent is obese, and on the timing of obesity (pre-conceptional or maternal at gestation) (59). These trans-generational consequences emphasise a need for life-course epidemiologic studies to unravel the causal relationships between early life events, including the timing of maturation and adiposity during growth and in adulthood, and the development and progression of cancer. This is particularly necessary in view of the contrasting policy implications of the divergent effects of greater growth on cardiovascular disease and cancer risk (19).

While there is growing evidence that risk of some cancers increases with greater adiposity (see Table 1) (1), the relevant critical periods throughout the life course are not fully understood. For example, the association between body weight and composition and breast cancer risk is complex. Higher birth weight is associated with increased risk, and higher adiposity during adolescence and young adulthood with decreased risk of premenopausal cancer, but also with increased risk of postmenopausal cancer (58, 60) (although this pattern is not observed across all ethnicities (61)). This poses major challenges for epidemiologic studies, because complete understanding of these associations would require a longitudinal design with multiple measures of body weight and composition from birth to adulthood, which is generally not feasible. Another option is to rely on recall of self-reported body size at different time periods, which may lead to misclassification and bias. There are other markers of body size in adolescence such as Stunkard scales (62), which have revealed a link between body size and subsequent cancer risk (63, 64), and growth trajectories associated with elevated cancer risk (65). It is clear that at

least for breast cancer, weight and body composition at critical periods (for example the prenatal period, at birth, in early childhood and in adolescence) is important to consider when evaluating contemporaneous body size. Further, it is suggested that obesity at critical stages of breast tissue evolution may compound oestrogenic effects (43). For other cancers, these critical periods are not well known.

Anthropometric measures, sex, and race/ethnic variation

A final consideration in the relationship between the commonly used anthropometric markers of adiposity and cancer risk is that this relationship varies between sexes and among racial/ethnic groups (61, 66). At the same BMI level, women tend to have higher body fat percentage compared with men (67). BMI and other anthropometric variables have differential associations by sex with risks for some cancers including colon, gallbladder, renal, and pancreatic cancers (9).

Several studies across the world have shown that body composition varies by race/ethnicity (21), and variations in the relationship between BMI and body fat percentage have been observed between Caucasian, African and Asian populations (68, 69). In addition, body composition and fat distribution appear to vary for different race/ethnic groups at similar BMIs (69-71). For example, Asian Indian men with a BMI of 24 kg/m^2 and women with a BMI of 26 kg/m^2 have the same percentage body fat as European adults with a BMI of 30 kg/m^2, or Pacific men and women with BMI of 34 and 35 kg/m^2 respectively (69). Additionally, race/ethnic variation in metabolic biomarkers is apparent after controlling for BMI (72). For example, Asians have higher metabolic risk than Europeans at a given BMI, waist circumference or waist-to-hip ratio (69, 73). This may contribute to observed ethnicity-related differences in cancer risk at similar levels of anthropometric measures of adiposity.

Thus, BMI represents different levels of adiposity and associated metabolic risk in different racial/ethnic groups. Specific cut-off points for comparison of obesity prevalence across ethnic groups have been proposed to reflect this (21). In a recent meta-analysis on adiposity and premenopausal breast cancer (61), ethnicity was the largest source of heterogeneity in the results. BMI was inversely related to premenopausal breast cancer among Caucasian and African women, while no association was observed among Asian women. When considering waist-to-hip ratio, the strongest risk was observed among Asian women (19% increased breast cancer risk per 0.1 unit increase) while the risk was lower among African and Caucasian women (5% and 6%, respectively) (61). Variability in whole adipose tissue proportion and distribution according to ethnicity, and associated metabolic risks, need to be considered when conducting and interpreting results in epidemiologic studies.

CONCLUSIONS

In conclusion, obesity remains a major public health concern; of the various nutritional and dietary exposures evaluated in the WCRF/AICR Second Expert Report (1) and Continuous Update Project (2), anthropometric markers of adiposity have been found to be most strongly and consistently associated with the development and progression of several cancers. The current state of knowledge provides a strong basis for a public health recommendation to avoid excess adiposity in order to reduce cancer risk in adulthood.

However, these findings arise from data and tools that are limited. Many measures are interrelated, and it is often unclear how any individual marker relates to body composition, the growth trajectory, maturation, or the internal physiologic or metabolic milieu. Specifically, it is essential to better characterise adiposity and the regional distribution of adipose tissue, as well as its site of deposition within or outside the abdominal cavity. It is also critical to understand how such aspects of

adiposity relate to other important markers of growth and maturation, and what the relevant susceptible periods throughout the life-course are for different cancers. A clearer understanding of the biological pathways (physiological, metabolic, or at whole body or cellular levels) that underpin the links between body weight, size and composition through the life-course and risks of specific cancers will help to generate improved evidence on which to base public health policy and clinical management approaches for cancer prevention. This may be achieved through better integration of metabolic, clinical and laboratory studies with nutritional epidemiology. With numbers of cancers predicted to increase throughout the world over the next decades, and obesity on the rise in many developing countries particularly, coherent preventive policies that address cancer prevention during the epidemiologic transitions are essential. Although care is needed in their interpretation, existing anthropometric measures are useful tools for understanding the links between body size and composition and cancer. Future research on specific aspects of body composition that are linked to risk of cancer (and other chronic diseases) may help refine the use of anthropometry in this field.

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Table 1. Cancer sites with strong evidence in the WCRF Continuous Update Project for an association between cancer risk and body fatness (adiposity), adult weight gain or adult attained height

Cancer site	Body mass index	Waist circumference	Waist-hip ratio	Adult weight gain	Adult attained height	Ref
Stomach (cardia)[1]	↑					(74)
Kidney[1]	↑↑	↑↑	↑↑		↑	(75)
Gallbladder[1]	↑					(76)
Liver[1]	↑↑					(77)
Prostate (advanced)[1]	↑	↑	↑			(78)
Ovarian[1]	↑				↑↑	(79)
Endometrial[1]	↑↑	↑		↑		(80)
Pancreatic[1]	↑↑	↑↑	↑↑	↑↑	↑	(81)
Colorectal[2]	↑↑	↑↑	↑↑		↑↑	(82)
Breast (postmenopausal)[3]	↑↑			↑	↑↑	(83)
Breast (premenopausal)[1]	↓				↑	(83)
Oesophageal (adenocarcinoma)[1]	↑↑					(1)

↑↑ convincing increased risk; ↑ probable increased risk; ↓ probable decreased risk. See supplementary information for definitions.

[1]Judgement of 'body fatness'

[2]Judgement of 'body fatness' and 'abdominal fatness'

[3]Judgement of 'body fatness', 'abdominal fatness' and 'adult weight gain'