1 The use and interpretation of anthropometric measures in cancer epidemiology: A
2 perspective from the World Cancer Research Fund International Continuous Update
3 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.

54 INTRODUCTION

55 Since the early 1980s, evidence has accumulated from a rapidly growing body of
56 epidemiologic studies (1, 2) showing an association between increased adiposity and
57 the risk and progression of cancer. This association is supported by clinical studies
58 (3, 4), which together with a better understanding of the biology of cancer (5) have
59 helped to identify mechanisms through which energy balance might influence the
60 cancer process. Together, this evidence supports a causal association between
61 increased adiposity and cancer occurrence (1, 2, 6).

62
63 Anthropometric measures reflecting body size and composition have been
64 associated with site-specific cancer development (1), with growing evidence that
65 body composition plays important role in cancer treatment, side effects and survival
66 (7). These measures include height, weight and waist and hip circumference, and
67 derived indices such as BMI, waist-to-hip ratio and waist-to-height ratio. Measures of
68 birth size and weight, growth during childhood (sometimes linked with measures of
69 maturation such as age at menarche or menopause), and/or change in weight in
70 adulthood have also been considered if available. However, the precise relationships
71 between these variables are often poorly characterised (8). Furthermore, these
72 measures are subject to additional limitations in that they mask the processes
73 underlying observed associations, such as developmental factors that may give rise
74 to critical periods of susceptibility where intervention would be most beneficial.
75 Measures that do not distinguish lean from adipose tissue may also obscure any
76 separate roles of low lean mass and high adiposity in determining cancer risk.
77 Consequently, it is important to be aware of the advantages and limitations of using
78 anthropometry to unravel precise causal connections between nutritional state and
79 cancer, particularly when using these to make clinical and public health
80 recommendations.

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

92

93 **ANTHROPOMETRIC FACTORS AND CANCER: ASSESSING THE EVIDENCE**

94 **The role of epidemiologic studies**

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

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

114

115 [Table 1 about here]

116

117 **Key challenges in evaluating the impact of adiposity on cancer risk**

118 Studies related to adiposity represent a unique challenge in epidemiology. Most
119 epidemiologic studies have used anthropometric measures such as BMI, weight
120 change over a specified time, and body circumference measures as markers of body
121 composition. Although such markers are imperfect, and may reflect genetic and other
122 non-nutritional factors, at a population level markers of adiposity (e.g., higher BMI or
123 waist circumference) are strongly correlated with systemic and tissue factors that
124 may potentially influence cancer, such as systemic low-grade inflammation,
125 oestrogen levels in postmenopausal women, insulin resistance and hyperinsulinemia
126 (9).

127

128 Adipose tissue in humans is a structural and thermal buffer, a store of energy in the
129 form of lipid (principally triglycerides), and an active endocrine organ involved in
130 hormonal secretion and metabolism that contributes to appetite regulation, immune
131 function and inflammation (10, 11). Abdominal visceral adipocytes are more
132 metabolically active than abdominal subcutaneous adipocytes, as they have high
133 lipolytic activity and release large amounts of free fatty acids (12, 13). Some studies
134 have shown that for certain cancers, abdominal obesity may be associated with risk
135 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).

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

168

169 **Limitations of current anthropometric measurements**

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

178

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

191
192 Epidemiologic studies often rely on self-reported height and weight which may
193 include systematic errors in calculations of BMI; people tend to under-report weight
194 and over-report height (28). However, studies have shown a strong correlation (>0.9)
195 between self-reported and measured weight and height (29-32). Furthermore, the
196 impact of such systematic measurement error on relative risk estimates in
197 epidemiologic studies is generally small (33). BMI cut-offs are therefore useful at the
198 population level, but may not accurately reflect adiposity of individuals.

199
200 Furthermore, comparison across studies examining cancer risk according to BMI is
201 problematic if studies have assessed risk across specified quantiles. As the
202 distribution of BMI varies between populations, at different stages of life and different
203 time periods, the specific groupings may not be comparable. Other studies report risk
204 according to WHO BMI categories, which may mask associations within these
205 categories.

206
207 **Measures of adipose distribution** typically include waist and hip circumferences,
208 waist-to-hip ratio and waist-to-height ratio. Waist and hip circumference
209 measurements show greater inter-observer variability than assessments of weight or
210 height. This is in part attributed to the lack of a standardised methodology for
211 measuring waist and hip circumference (21). However, these measures are useful to
212 identify abdominal obesity, commonly defined as a waist-hip ratio of ≥ 0.90 for males
213 and ≥ 0.85 for females, with waist measurement cut-offs varying according to sex and
214 ethnicity (21). However these measures cannot differentiate between visceral and
215 subcutaneous adipose compartments (34). Visceral adiposity is positively related to
216 cardiovascular disease, metabolic syndrome, type 2 diabetes, and several types of
217 cancer (35-37), whereas subcutaneous adipose tissue has an anti-atherogenic effect
218 (13). The associations of these different adipose tissue compartments are less well

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

222
223 **Weight change.** The association of weight gain and loss with cancer risk has been
224 evaluated in many studies and presents additional challenges.

225
226 Weight gain throughout adulthood has been shown in the literature to increase risk of
227 several cancers, such as postmenopausal breast cancer, endometrial, ovarian
228 cancer, colon cancer, prostate cancer and kidney cancer (39, 40). The Continuous
229 Update Project has confirmed this link in endometrial, pancreatic and
230 postmenopausal breast cancers (see Table 1). Weight gain may be a better marker
231 of adiposity than BMI because it represents a snapshot of the weight trajectory
232 throughout adult life, which in most adults results in accumulation of adipose tissue
233 (39). However, the assessment of weight gain in most studies has been based on
234 recall, which may have led to measurement error, but generally expected to be
235 random and resulting in attenuation of effect estimates (39).

236
237 Intentional weight loss has been associated with reduced risk of cancer (41, 42),
238 providing further support for a link between excess adiposity and disease risk. This
239 type of evidence has been challenged, however, (43) meaning that caution must be
240 exercised when interpreting data on weight in isolation. Furthermore, information on
241 the intervention for weight loss is not always clearly reported, additionally clouding
242 the findings. Notably, intentionality of weight loss cannot always be included
243 alongside measurements. The possibility of “reverse causation”, resulting from
244 undiagnosed pre-clinical disease or other chronic illness leading to weight loss, may
245 produce spurious findings. One way to avoid this bias is to exclude subjects with
246 serious illness and weight loss during the first few years of follow-up (44). However,

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

254

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

262

263 More direct and sophisticated measures of adiposity are available, such as air
264 displacement plethysmography, underwater weighing (hydrodensitometry), dual-
265 energy X-ray absorptiometry, ultrasound, computed tomography and magnetic
266 resonance imaging (47). These methods show excellent reproducibility and validity
267 (48, 49) and are increasingly being employed to measure adiposity at the tissue or
268 organ levels, particularly in small-scale studies that require a high level of accuracy.
269 However, due to high costs and lack of portability, their use in large-scale
270 epidemiologic studies has been limited.

271

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

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

281

282 **Anthropometry throughout the life-course**

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

290

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

302

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

315
316 While there is growing evidence that risk of some cancers increases with greater
317 adiposity (see Table 1) (1), the relevant critical periods throughout the life course are
318 not fully understood. For example, the association between body weight and
319 composition and breast cancer risk is complex. Higher birth weight is associated with
320 increased risk, and higher adiposity during adolescence and young adulthood with
321 decreased risk of premenopausal cancer, but also with increased risk of
322 postmenopausal cancer (58, 60) (although this pattern is not observed across all
323 ethnicities (61)). This poses major challenges for epidemiologic studies, because
324 complete understanding of these associations would require a longitudinal design
325 with multiple measures of body weight and composition from birth to adulthood,
326 which is generally not feasible. Another option is to rely on recall of self-reported
327 body size at different time periods, which may lead to misclassification and bias.
328 There are other markers of body size in adolescence such as Stunkard scales (62),
329 which have revealed a link between body size and subsequent cancer risk (63, 64),
330 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/m² and women with a BMI of 26 kg/m² have the same percentage body fat as European adults with a BMI of 30 kg/m², or Pacific men and women with BMI of 34 and 35 kg/m² 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.

368

369 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.

377

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.

400

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Accepted Article

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.

¹Judgement of 'body fatness'

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

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

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