



Obesity and Cancer: Optimizing Risk Assessment

Edward R. Sauter, MD, PhD

Division of Cancer Prevention, NCI/NIH, Rockville, MD

OVERVIEW

This perspective addresses the issue of obesity, adiposity (obesity) measures, and their use in online cancer risk assessment tools. Our focus is on healthy individuals (no known cancer nor a clinically suspicious finding that requires investigation). Other cancer assessment tools, such as nomograms that have been developed to assess response to cancer treatment and those that help determine when and if to perform cancer screening, are not addressed in this report.

Health care providers deliver patient care for common diseases such as diabetes, cardiovascular disease (CVD), and cancer. There are readily available online tools to assess diabetes and CVD risk. Cancer risk assessment tools are not as standardized, in part because different tools target either the general public or health care providers.

Obesity, a growing problem that is modifiable, increases the overall incidence of 13 cancers (meningioma, esophageal adenocarcinoma, multiple myeloma, kidney cancer, endometrial cancer, ovarian cancer, colorectal cancer, pancreatic cancer, upper gastric cancer, gallbladder cancer, liver cancer, postmenopausal breast cancer, and thyroid cancer) and aggressive prostate cancer.¹ Risk assessment tools have limited or no assessment of obesity related variables. When present, the only tool generally included is

body mass index (BMI), a suboptimal obesity measure. Multiple studies suggest that including one or more obesity measurements in the assessment of an obesity related cancer improves the assessment tool.^{2,3}

BODY MASS INDEX ALONE MAY NOT OPTIMALLY ASSESS A PERSON'S OBESITY-ASSOCIATED CANCER RISK

Fat accumulates subcutaneously, around muscles, and around intra-abdominal organs (viscerally). Visceral adipose tissue (VAT) more accurately predicts metabolic dysfunction than subcutaneous fat and BMI.⁴ BMI does not differentiate muscle versus fat mass, does not fully characterize the biology and physiology of excess body fat, and is inaccurate to evaluate: (1) the elderly, who may lose height and/or develop aging-related sarcopenia; (2) individuals of Asian descent; (3) the difference between fat and lean mass; (4) individuals of extreme height; (5) very muscular individuals; and (6) individuals with excess adiposity who are of normal weight.⁵ There are multiple clinical assessments of obesity other than BMI, including weight gain, waist circumference, waist-to-hip ratio, waist-to-height ratio, waist-to-hip-to-height ratio, percentage body fat,⁶ and combinations of these measures,^{6,7} which focus at least in part on VAT. Imaging using dual energy x-ray absorptiometry,⁸ computed tomography (CT), and magnetic resonance imaging (MRI) are more accurate than clinical tools, but involve cost and ionizing radiation (CT).

RISK ASSESSMENT OF OBESITY-RELATED CANCERS

Risk assessment tools are most often accessed by both health care providers and patients using the internet. While the greatest breadth of information available for an online tool is through an internet search, increasingly applications (apps) have been and are being created due to their ease of use. A recent review identified six commonly used apps

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First Received: 9 September 2022

Accepted: 11 October 2022

Published Online: 30 October 2022

E. R. Sauter, MD, PhD
e-mail: edward.sauter@nih.gov

available in English through Google Play and/or the App Store for use on Android and/or iOS systems and applicable to healthy individuals in North America and Europe of European descent to assess the risk of developing one or more obesity-related cancers.⁹

TOOLS THAT ASSESS OVERALL CANCER RISK OR RISK OF MULTIPLE INDIVIDUAL CANCERS

These cancer risk assessment tools are more often qualitative than quantitative. They are often geared toward individuals who want a general idea of their overall risk, and possible ways to reduce their risk. For example, ‘The Defender’ tool (American Cancer Society: <https://thedefender.cancer.org>) and the ‘WCRF Cancer Health Check’ (World Cancer Research Fund: <https://www.WCrf-uk.org/>) provide recommendations based on an individual’s responses on how to modify one’s lifestyle to lower cancer risk. The ‘Cancer Risk Calculator’ (<https://play.google.com/store/apps>) provides 10, 20, 30 years, and lifetime overall and individual cancer risk. Siteman Cancer Center’s ‘Your Disease Risk’ (<https://siteman.wustl.edu/prevention/ldr>) provides risk assessment (ranging from low to high) for a variety of cancers. ‘Your Disease Risk’ includes the assessment of BMI, weight change from age 18 years to current age, and body shape at age 7 years. Cancer Care Ontario’s ‘What’s My Risk’ also provides risk assessment (low to high) for a variety of cancers (<https://www.myca.nceriq.ca>).

ASSESSMENT OF SINGLE OBESITY-RELATED CANCERS

Risk assessment tools of single site-specific cancers are often more quantitative than overall cancer risk assessment, providing a percentage risk of developing the cancer over a given time period. PubMed and Google searches were performed by the author. In addition, searches of the PubMed, Scopus, Web of Science, Embase, and CINAHL databases were performed by an informationist at the National Institutes of Health library. Search terms used by the librarian included: quantitative or year or score or numeric; risk assessment tool or nomogram; cancers: endometrial cancer, esophageal adenocarcinoma, gastric cardia cancer, liver cancer, kidney cancer, multiple myeloma, meningioma, pancreatic cancer, colorectal cancer, gallbladder cancer, breast cancer, ovarian cancer, thyroid cancer, and prostate cancer. Search results are outlined in Table 1. The searches did not identify a risk assessment tool focused on a single site-specific cancer with obesity measures other than BMI.

We identified online risk assessment tools for 8 of the 14 (13 related to overall risk, prostate to aggressive disease) obesity related cancers (Table 1). We did not identify an online tool for the following 6 cancers: meningioma, multiple myeloma, upper gastric cancer, gallbladder cancer, liver cancer, and thyroid cancer. Exceptions are for high incidence areas for gallbladder cancer (India, Chile, and Japan)¹⁰ and liver cancer (sub-Saharan Africa and Southeast Asia).¹¹

CAN CANCER RISK ASSESSMENT BE IMPROVED?

This is a desirable goal. Non-obesity factors have been added in some cases, for example adding the assessment of breast density in more recent versions of Tyrer–Cuzick and other risk assessment platforms. Challenges to improving risk assessment tools with obesity related factors include (1) analysis of cancer cohorts of sufficient size and length of follow-up that have a variety of obesity measures; (2) determining where in the life course obesity should be accounted for; (3) incorporating measures that have been collected in all or most individuals within the cohort under study; (4) assessing the quality of a risk assessment tool; and (5) convincing health care providers and individuals to know about, have access to, and to use the tool. Some of these factors are briefly discussed below.

Some assessed measures have not and will not improve the risk model. Indeed, weight change later in life was not found to predict colorectal cancer risk among participants in a European Prospective Investigation into Cancer cohort study.¹² Nonetheless, more investigation is needed into the possible risk assessment benefit of evaluating obesity measures other than BMI for all obesity related cancers. Obesity information available for many of the largest cohort studies is provided in Table 2. Both cohort and disease sample size limitations are challenges for many cancers and may help explain why online risk assessment tools are not available for six cancer types in Table 1. Table 1 also contains some commonly used tools that require special software not currently available online, as well as a promising tool that uses artificial intelligence to predict breast cancer risk.

The most accurate VAT measures (CT and MRI) are generally not available in sufficient numbers in any existing cohort to be incorporated into a risk assessment model. Moreover, it should be possible to assess the accuracy of the tool. Since the internet is unregulated, this is especially important. Investigators at Harvard and the University of Pennsylvania searched the internet to identify all internet cancer risk calculators, reviewing the content of each site for information that could be used to evaluate the website’s

TABLE 1 Risk assessment tools focused on a single obesity related cancer among healthy (non-cancer containing) individuals

Cancer	Guidelines		Do the guidelines assess obesity?	If Y, how?
	Y/ N	If Y, example guidelines		
		CCRAT		
Colon and rectum	Y	Cleveland clinic	Y	BMI
Pancreas	Y	Your disease risk	Y	BMI
Ovary	Y	Your disease risk	Y	BMI
Postmenopausal breast	Y	BCRAT	Y	BMI
		Tyrer-Cuzick	Y	BMI
		BH-BCRA	Y	BMI
		CS-BHA	Y	BMI
		BOADICEA	Y	BMI
		Claus	N	
		Breast Cancer Surveillance Consortium Risk Calculator	N	
Kidney cancer	Y	What's My Risk	Y	BMI
		Your Disease Risk	Y	BMI
Adenocarcinoma of the esophagus	Y	IC-RISC	N	
Endometrium	Y	Your Disease Risk	Y	BMI
Prostate	Y	PCPT	N	
Meningioma	N			
Multiple myeloma	N			
Upper gastric	N			
Upper gastric	N			
Liver	N			
Thyroid	N			
<i>Examples of risk models not readily available online but frequently discussed</i>				
Breast	Y	BRCAPRO		Software available for purchase
Breast	Y	Mirai		MIT's Computer Science and Artificial Intelligence Laboratory

CCRAT Colorectal Cancer Risk Assessment Tool, BCRAT Breast Cancer Risk Assessment Tool, BOADICEA Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, BH-BCRA Beaumont Health Breast Cancer Risk Assessment, BRCAPRO tool to assess risk of carrying a mutation in BRCA1 or BRCA2 gene, CS-BHA Cedars Sinai Breast Health Assessment, IC-RISC Interactive and Contextual Risk Calculator, PCPTRC Prostate Cancer Prevention Trial Risk Calculator. Y/N refers to whether obesity is assessed in the tool

quality.¹³ Their review determined that most sites do not provide the information needed to determine the website's legitimacy.

Health care providers, their patients, and other individuals need to know where to find accurate, reliable, and easy-to-use risk assessment tools. They need ready access to risk assessment tools from sites that are free and trustworthy, such as government and non-profit or medical/healthcare society sites. Risk assessment tool apps are available for some tools but not all.

Our review of large cohort studies (Table 2) demonstrates that weight change (gain or loss), waist circumference, hip circumference, and/or body shape were collected in multiple studies. At least two (Multiethnic Cohort and German National Cohort) studies are now collecting CT and MRI data. The German National Cohort is also performing body impedance analysis and ultrasounds to assess abdominal fat distribution.¹⁴ Clinical assessment of waist circumference, hip circumference, and weight change now seems practical for assessment for many cohorts.

TABLE 2 Obesity information available in large cohort studies

Study name	Adiposity measures	Enrollment	Website
Agricultural Health Study	wt, ht	83028	http://aghealth.nih.gov/
Breast Cancer Family Registry Cohort	wt, ht	40029	http://www.bcfamilyregistry.org/
Cancer Prevention Study II Nutrition Cohort	wt, ht	184185	https://www.cancer.org/research/we-conduct-cancer-research/epidemiology/cancer-prevention-study-2
Clue Cohort Study- Clue II	wt, ht	32893	http://www.jhsph.edu/comstockcenter/clue_research_activities.html
Colon Cancer Family Registry Cohort	wt, ht, wt Δ	37436	http://www.coloncfr.org/
European Prospective Investigation in Cancer and Nutrition	wt, ht, wc, wc/hc	521323	http://epic.iarc.fr/
German National Cohort	wt, ht, wc, hc, BIA, US, MRI	200000	https://www.dkfz.de/en/forschung/index.html
Health Professionals Follow-up Study	ht, wt, wt Δ	51529	http://www.hsph.harvard.edu/hpfs/
Janus Serum Bank	bmi	318628	http://www.krefregisteret.no/en/Research/Janus-Serum-Bank/
Melbourne Collaborative Cohort Study	wt, wc	41,500	https://www.pedigree.org.au/pedigree-studies/health2020.aspx
Millennium Cohort Study Panel 1	ht, wt	77010	http://millenniumcohort.org/
Millennium Cohort Study Panel 2	ht, wt	31101	http://millenniumcohort.org/
Millennium Cohort Study Panel 3	ht, wt	43429	http://millenniumcohort.org/
Millennium Cohort Study Panel 4	ht, wt	50043	http://millenniumcohort.org/
Multiethnic Cohort Study	wt, ht, wc, wc/hc, wt Δ , on subset of 1860 pts: VAT by DEXA and MRI	215251	http://www.uhcancercenter.org/research/the-multiethnic-cohort-study-mec
Nurses' Health Study	ht, wt, wt Δ	121601	http://www.nurseshealthstudy.org/
Nurses' Health Study II	ht, wt, wt Δ	114496	http://www.nurseshealthstudy.org/
Physicians' Health Study I and II	ht, wt, wt Δ	29071	http://phs.bwh.harvard.edu/
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	wt, ht, wc/hc (qualitative), wt Δ	154896	https://biometry.nci.nih.gov/cdas/plco/
Sister Study	ht, wt, wt Δ	50884	http://sisterstudy.niehs.nih.gov/English/index1.ht
Southern Community Cohort Study	ht, wt, wc, hc, bw	85401	https://www.southerncommunitystudy.org/
Swedish Mammography Cohort	wt, ht, wc, hc, body shape age 10, bw	61371	https://snd.gu.se/en/catalogue/study/ext0018
Swedish National March Cohort	ht, wt, wc, hc, bw	43804	http://ki.se/en/meb/the-swedish-national-march-cohort-nmc
UK Biobank	wt, ht, wc, wc/hc	502682	https://www.ukbiobank.ac.uk/
The Melbourne Collaborative Cohort Study	ht, wt, wc, hc, BIA	41514	http://www.pedigree.org.au/pedigree-studies/health2020.aspx
The National Institutes of Health AARP Diet and Health Study	ht, wt	373096	http://dietandhealth.cancer.gov/

wt weight, ht height, wc waist circumference, hc hip circumference, wt Δ weight change as an adult, BIA bioelectric impedance analysis, bw birth weight, wc/hc waist/hip circumference ratio, VAT visceral adipose tissue, DEXA dual energy X-ray absorptiometry, MRI magnetic resonance imaging, US abdominal ultrasound

In conclusion, BMI is the only adiposity measure incorporated for online readily accessible tools that evaluate a single cancer and provide quantitative risk assessment. Our findings suggest that additional effort should be strongly considered to evaluate clinical VAT

measures of obesity in addition to BMI for their potential value in improving cancer risk assessment tools. New large cohorts such as the National Institutes of Health supported million plus person *All of Us* study (<https://allofus.nih.gov>)

could incorporate obesity measures other than BMI to assist in future efforts to improve assessing the role of obesity in cancer risk.

AUTHOR CONTRIBUTION ES conceived the design of this study and prepared the manuscript.

DISCLOSURE The author declares no conflict of interest.

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