Commentary

Cancer Epidemiology, Biomarkers & Prevention

Excess Weight as a Risk Factor Common to Many Cancer Sites: Words of Caution when Interpreting Meta-analytic Evidence

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For over a decade, excess body weight, commonly categorized as overweight [body mass index (BMI): 25.0–29.9 kg/m^2] and obesity (BMI: $\geq$30 kg/m^2), has been an established incidence risk factor for several adult cancers (1). For 2012, the burden of disease attributed to elevated BMI was estimated as nearly a half million new cancers worldwide, making this the third highest ranked cancer risk factor globally after smoking and infections (ranked second in most Western populations) and an important public health problem (2, 3). In recent years, scientific evidence on BMI–cancer associations has continued to accumulate and reveals positive associations for even more and more cancer sites. Among the most comprehensive and systematic evaluations undertaken on these associations have been through the World Cancer Research Fund (WCRF) Continuous Update Project, which now links excess weight or body fatness to 11 cancers (4). In 2016, an expert working group of 21 scientists from eight countries gathered under the auspices of the International Agency for Research on Cancer (IARC) to evaluate the preventive effects of avoidance of excess body fatness on cancer risk. This group extended the list of obesity-related cancers, for which sufficient evidence exists, to 13 as follows: cancers of the colon and rectum, esophagus (adenocarcinoma), kidney (renal cell), breast (postmenopausal), endometrium, gastric cardia, liver, gallbladder, pancreas, ovary, thyroid, multiple myeloma, and meningioma (5). Considering that excess body adiposity is related to a vast array of metabolic and physiologic dysfunctions, underlying biological mechanisms have been identified explaining many of these associations (6). Furthermore, these cancer sites together represent more than one third of the total global cancer burden (7), suggesting a large prevention potential.

The identification and extraction of summary risk estimates from systematic reviews and meta-analyses evaluating anthropometric measures and cancer risk constitute an important part of the total integration of evidence judged in the aforementioned overviews. Indeed, there has been a near exponential expansion of meta-analyses in this field. In general terms, updating or refining of existing meta-analyses or building a meta-analysis on a previously understudied area is a positive thing. Thus, for example, where interventions (e.g., drug administration) have been tested in randomized controlled trials (RCT), the meta-analysis of several small trials might reveal a more precise estimate of effect and build a greater degree of certainty that that intervention is clinically effective. Ultimately, a threshold number of RCTs might be reached at which the evidence of effect is convincingly strong, and no further RCTs are required; this is known as cumulative meta-analysis (8).

However, this principle might not apply for the evaluation of obesity–cancer associations, as analyses in many observational studies are well powered. The main methodologic issue is generally not the need to increase estimate precision (as for RCTs) but rather to explore sources of between-study heterogeneity. During the IARC handbook writing group evidence evaluation (5), the current authors (as part of that group) encountered some new pitfalls regarding meta-analyses that evaluated obesity–cancer associations and use this commentary to share these cautions when interpreting these lines of evidence.

First, meta-analyses conducted as part of systematic reviews can be subject to a form of publication bias, which we have termed as same framework differential study identification bias. Here, "same framework" might refer to same time frame or same population (e.g., a systematic review might be restricted to a specific race). Thus, during evaluation, the IARC working group referred to the WCRF bladder cancer report based on 22 prospective cohort studies, which reported no significant association between obesity and bladder cancer incidence (9), but two additional meta-analyses of prospective cohort studies (10, 11), searching very similar timeframes, identified substantially different study numbers. These analyses reported significant positive associations and (in contrast to the WCRF analysis) concluded that BMI was associated with an increased risk of bladder cancer (Table 1). On closer scrutiny, these differences partly reflect obscure decisions about study inclusion (despite that the design type was restricted to prospective studies) and, in the meta-analysis by Sun and colleagues (11), the summary estimate may have been disproportionally influenced by an incorrect data extraction of risk estimates from one study (12). In addition, one large analysis from the EPIC cohort (13), reporting a mildly elevated risk of bladder cancer in overweight when compared with normal weight men, was not included in the systematic review by Sun and colleagues (11) that searched within the timeframe of this publication (epub date: April 29, 2014). In a similar manner, a recently published meta-analysis (14) evaluating the association between BMI and cervical cancer risk identified only nine studies (Table 1), yet the IARC handbook group search, over a similar timeframe, identified 14 studies (listed in Supplementary Material). On the basis of arguably an under-captured number of studies, the former concluded that obesity might be associated with increased risk of cervical cancer.

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Table 1. Summary of meta-analyses evaluating the association between BMI and incident bladder and cervical cancers

Authors, publication year	Search period	Number of studies	Summary risk estimates (95% confidence intervals)	Conclusions
Bladder cancer				
Qin et al. 2013 (10)	To March 10, 2013	11 prospective	Obese vs. normal: 1.10 (1.06–1.16)	"...obesity is associated with the increased risk of bladder cancer"
Sun et al. 2015 (11)	To Sept. 30, 2014	15 prospective	Overweight vs. normal: 1.07 (1.01–1.14)[a] Obese vs. normal: 1.10 (1.06–1.14)[a]	"...obesity is associated with linear increased risk of bladder cancer"
WCRF report 2015 (9)	To July 9, 2014	22 prospective	Per 5 kg/m^2: 1.03 (0.97–1.09)	Limited evidence, no conclusion
Cervical cancer				
Poorolajal and Jenabi 2016 (14)	To February 2016	2 cohorts	Overweight vs. normal: Case–control: 1.03 (0.81–1.25) Cohorts: 1.10 (1.03–1.17)	"...overweight is not associated with an increased risk of cervical cancer, but obesity is weakly associated with an increased risk of cervical cancer"
		5 case–control	Obese vs. normal: Case–control: 1.40 (1.08–1.71)	
		2 cross-sectional	Cohorts: 1.08 (0.60–1.52)	

[a]In the Sun et al. (11) meta-analysis, the extracted point estimates relative to normal weight from Song et al. (12) for BMI categories 25.0 to 27.4, 27.5 to 29.9, 30.0 to 34.9, and greater than or equal to 35.0 kg/m^2 for men were 1.48, 1.95, 1.47, and 1.91, respectively, and for women were 2.59, 2.69, 2.63, and 1.93, respectively. Yet, the continuous BMI plots in Fig. 1 of Song et al. (12) indicate that the BMI–risk relation was absolutely null, with risk near 1.00 across the full BMI range.

Second, the above-illustrated publications raise the concern that, in addition to the typical study-level publication bias normally assessed within a systematic review, there is the potential for review-level publication bias. This can be partly tested for within the context to umbrella reviews and the use of excess statistical significance testing. Thus, for example, this approach has demonstrated an excess of statistically significant findings in meta-analyses of insulin-like growth factor (IGF)/insulin and inflammation systems and cancer risk (15), suggesting reporting biases. There is, therefore, a need for a more robust methodologic framework other than significant *P* value (and confidence intervals) and strengths of association for assessing evidence from meta-analyses. The nine Bradford–Hill criteria (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy) offer a starting point; the Bristol criteria (appropriate adjustment for key confounding factors, measurement error, assessment of residual confounding, and lack of alternative explanations; ref. 16) add a further dimension for assessing the causality of the evidence. Set within these principles, pathways for the association between excess adiposity and both bladder and cervical cancers are ill understood, and mechanistic evidence is lacking, such that significant summary estimate after meta-analyses (on their own) amounts to inadequate evidence of association.

Third, as cancer is frequently a multicausal disease, other common risk factors may modify or obscure an apparent relationship with obesity. One striking example of this is smoking status (17). Simple adjustment for smoking within a regression model may inadequately control for BMI–smoking interrelationships. Within meta-analyses and pooled analyses, there are more consistent approaches to test for confounding or effect modification (smoking may be both a confounder and effect modifier). Thus, for example, when the IARC handbook group (5) examined smoking-stratified analyses of the inverse associations between BMI and smoking-related cancers such as lung cancer and esophageal squamous cell carcinoma, null associations were generally observed in the never smoker strata. If study-level data are not reported by strata, an alternative approach might be to perform meta-regression of study-level hazards against the proportion of ever smokers per given population (1).

Meta-analyses of obesity–cancer associations have made important contributions to the understanding of cancer etiology and informing public health priorities. For this process to continue to move forward, investigators, peer reviewers, and editors need to be alert to the above biases and spurious associations. Continuing refinement to methods of reporting literature searches and article inclusion may be helpful, as advocated through reporting guidance for meta-analyses such as PRISMA statement (18). The value of pooled analysis of individual participant data, used commonly with clinical trials, shows promise to refine understanding when important confounders are present in the underlying data (19).

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No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Arnold, A.G. Renehan, G.A. Colditz
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Arnold, G.A. Colditz
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):, G.A. Colditz
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