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Obesity and cancer: An update of the global impact

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ABSTRACT

In view of the growing global obesity epidemic, this paper reviews the relation between recent trends in body mass index (BMI) and the changing profile of cancer worldwide. By examining seven selected countries, each representing a world region, a pattern of increasing BMI with region and gender-specific diversity is noted: increasing levels of BMI were most pronounced in the Middle East (Saudi Arabia), rather modest in Eastern Asia (India) and generally more rapid in females than in males. This observation translates into a disproportionate distribution of cancer attributable to high levels of BMI, ranging by sex from 4–9% in Saudi Arabia and from 0.2–1.2% in India. Overweight and obesity may also influence cancer outcomes, and hence have a varying impact on cancer survival and death in different world regions. Future challenges in cancer studies exploring the association with overweight and obesity concern the measurement of adiposity and its potentially cumulative effect over the life course. Given the limitations of BMI as an imperfect measure of body fatness, routine anthropometric data collection needs to be extended to develop more informative measures, such as waist circumference in settings where the gold standard tools remain unaffordable. Furthermore, questions surrounding the dose-response and timing of obesity and their associations with cancer remain to be answered. Improved surveillance of health risk factors including obesity as well as the scale and profile of cancer in every country of the world is urgently needed. This will enable the design of cost-effective actions to curb the growing burden of cancer related to excess body weight.

Contents

1. Introduction

The global prevalence of overweight and obesity (body mass index (BMI) $\geq$25 kg/m^2) has increased markedly over the past decades from 24.6% in 1980, to 34.4% in 2008. Over the same

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period, the prevalence of obesity (BMI $\geq$30 kg/m^2) has doubled, from 6.4% to 12.0% [1]. In many countries these changes have impacted on the main non-communicable diseases including heart disease [2], type 2 diabetes [2], as well as cancer [3–5]. Excess body weight has been causally linked to an increased risk of ten different cancer types, including cancer of the oesophagus (adenocarcinoma), colorectum, gallbladder, pancreas, liver, breast (post-menopausal), ovary, endometrium, kidney and prostate (advanced stage) [3,6–13]. These cancers alone (described hereafter as obesity-related cancers) comprise about 27% of the total global burden of cancer (based on GLOBOCAN 2012 data [14] and at present impact more on populations in highly-developed countries, where 67% of all obesity-related cancers are diagnosed. This observation is further confirmed by a recent study showing that 82% of all new cancer cases caused by excess body weight in 2012 were found in high income countries, as compared to only 18% in their lesser income counterparts [15].

Transitions in global cancer patterns have also been observed and have partly been linked to the growing obesity epidemic [16]. One example is the changing trends in oesophageal adenocarcinoma, a subtype of oesophageal cancer that is strongly associated with excess weight, with obesity increasing risk by greater than two-fold compared with normal weight [17]. Since the early-1990s, studies from high income countries such as the U.S. have noted a steep rise in the incidence of oesophageal adenocarcinoma, surpassing the incidence of oesophageal squamous cell carcinoma, which is related mainly to tobacco smoking [18]. At the global level, oesophageal adenocarcinoma now contributes 25% of the total oesophageal cancer burden in highly developed countries, in contrast to 6% in less developed countries [19].

In this paper, we provide an overview of the impact of overweight and obesity on the global burden of cancer. We link geographical and temporal patterns of BMI to the corresponding scale and profile of cancer, and quantify the number of new cancer cases attributable to high BMI in countries representing seven world regions. The challenges in surveillance of body composition in ethnically diverse populations are briefly summarized, and future research avenues on this basis discussed. We conclude with a perspective on specific actions required to curb the growing burden of cancers related to excess body weight, with a focus on locally-tailored strategies.

2. The growing obesity epidemic and its impact on the global cancer burden

Excess body weight has become one of the most important preventable causes of cancer, particularly in high-income countries [20]. Yet, the global observed epidemiologic and cancer transitions suggest the epidemic is also extending to transitioning countries in the less developed world [21,22]. Fig. 1 shows the average BMI in seven countries in 1980 and in 2008, selected based on availability of high quality data, regional representativeness and population size. Countries of the Middle East now have among the highest proportions of overweight and obesity in the world, with as an example an increase from 26.3 kg/m^2 to 29.6 kg/m^2 in the mean BMI between 1980 and 2008 in Saudi Arabian women. On the other hand, in India, South Asia, increases in average BMI have been limited over the past three decades. While the mean BMI since 1980 has increased slightly more rapidly in women than in males (0.5 vs. 0.4 kg/m^2 per decade), the rise in mean BMI in men tends to be greater in countries where BMI has been historically low, while the increase in women appears independent of past (or current) BMI levels in the same countries [23] (Fig. 2).

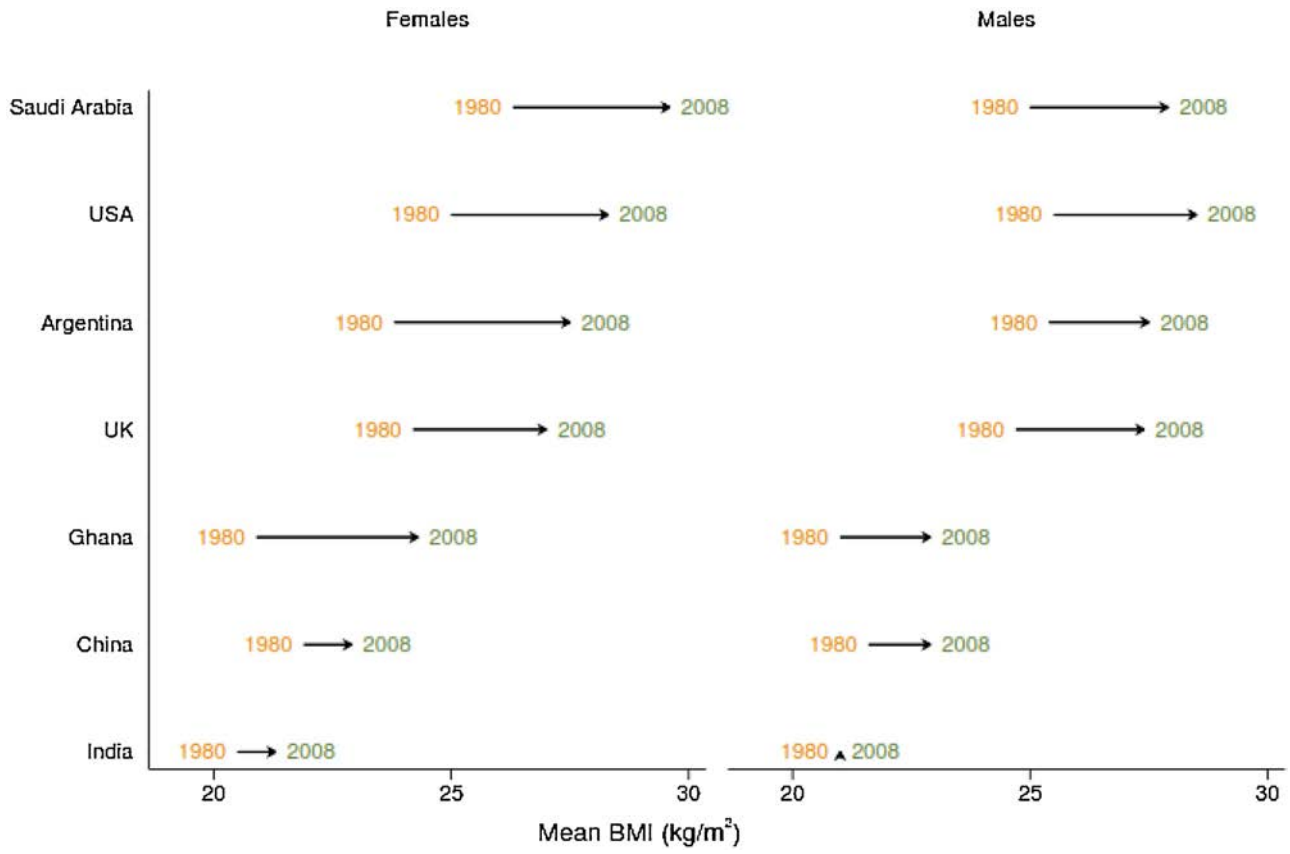

Fig. 1. Mean body mass index (age-standardized, in kg/m^2) in 1980 and in 2008 according to sex in selected countries [23].

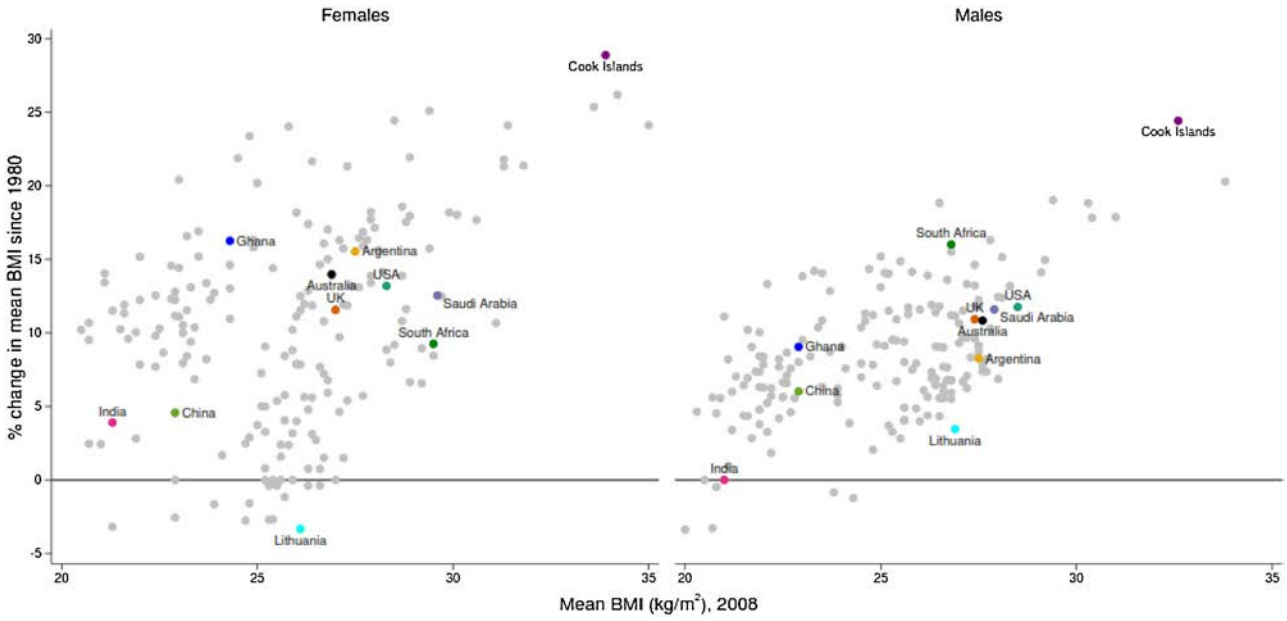

Fig. 2. Percent change in mean BMI between 1980 and 2008 versus BMI (in kg/m^2) in 2008.

Linking the global pattern of BMI to the cancer burden, the high average BMI in the Middle East is reflected by a high proportion of cancer attributable to high body weight (Saudi Arabia, 9.2% and 4.0% in females and males respectively, Fig. 3). Similarly, we observed a large proportion of obesity-attributable cancer burden in North America (USA, 9.5% and 3.5%) and in Europe (UK, 8.2% and 4.4%). This contrasts with the small proportion of cancer cases attributable to excess body weight in selected countries in sub-Saharan Africa (Ghana, 2.0% and 0.4%) and Asia (India, 1.2% and 0.2%). In terms of health planning, it is important to highlight the absolute number of cases that can be linked to high BMI, as illustrated in Fig. 3. In highly populous countries with an elevated prevalence of overweight individuals such as in the U.S., more than 100,000 new cancer cases in 2012 can be attributed to high BMI.

3. Global problem with regional diversity

Studies have reported a differential impact of high BMI on cancer risk across ethnic groups and geographic locations. For example, the protection from breast cancer conferred from overweight and obesity at premenopausal ages among Caucasian and African women is not reported in Asian women, where a significant deleterious effect has been observed [24]. In our previous paper [15], we recalculated the population attributable fraction (PAF) of overweight and obesity, replacing the pooled global risk estimates with regional relative risks (RR), concluding that region-specific PAF were similar to those obtained from the main analytic approach. Large differences were however found for postmenopausal breast and pancreatic cancer: the PAF of postmenopausal breast cancer due to high BMI in Asian females increased from 4–5% to 9–11% based on region-specific RR estimates. The varying effect of high BMI on cancer risk in different ethnicities has been postulated as a marker of the BMI's inability to measure body fatness and differentiate tissue type (fatty, lean, bone). Other anthropometric measures such as waist circumference or waist-to-hip ratio have been suggested to better predict obesity-related health outcomes when compared to BMI [25,26], despite their own limitations such as correct measurement, great inter-ethnic variability and the difficulty to interpret ratios biologically [27]. Where waist-to-hip ratio has been utilized, as in a study of premenopausal Asian women, a high ratio was associated with an elevated breast cancer risk [28]. Existing inconsistencies in the ability to predict disease across the different anthropometric measures may warrant the implementation of additional BMI cut-off points, as proposed by the WHO [29].

4. Challenges assessing body fatness and cancer risk in ethnically diverse populations

In order to derive an improved estimate of the global impact of overweight and obesity on the burden of cancer, a valid measure of body composition is needed. The reasons that BMI continues to be the most commonly used proxy for overall body fat in epidemiologic studies and clinical settings [30] are multiple: BMI is easy to calculate, data collection costs are low, and standardized cut-off points set by leading international and national institutions for classifying weight status of individuals based on their BMI, are available [31,32]. Despite these advantages, BMI is an indirect measure of adiposity and the inherent limitations are still to be fully appreciated in the research or clinical domain. It is well known that total body fat (general adiposity) and body fat distribution varies in different ethnic groups with similar BMI levels and that these variances are associated with differentials in disease risk [28]. For example, in Asians, higher rates of colorectal neoplasia are observed within the "normal" range of BMI as compared to Caucasians [33]. Furthermore, individuals with similar levels of BMI and general adiposity, may differ substantially in their body fat distribution [30], hypothesized reason to why BMI poorly predicts chronic disease risk at the individual level [34]. While the aetiology of obesity is always multifactorial, with both genetic and environmental components, a number of genetic variants contributing to obesity have been identified by large genome-wide association studies, that together were able to explain a modest fraction of the phenotypic variation [35]. While to-date most of those studies have been carried out in Caucasian populations, there is evidence for ancestry-based differences in genetic risk factors for obesity [36], which should be further addressed in investigations of gene-environment interactions.

Given the imperfections of BMI, waist circumference (WC) is often used in epidemiologic studies as a surrogate marker of body

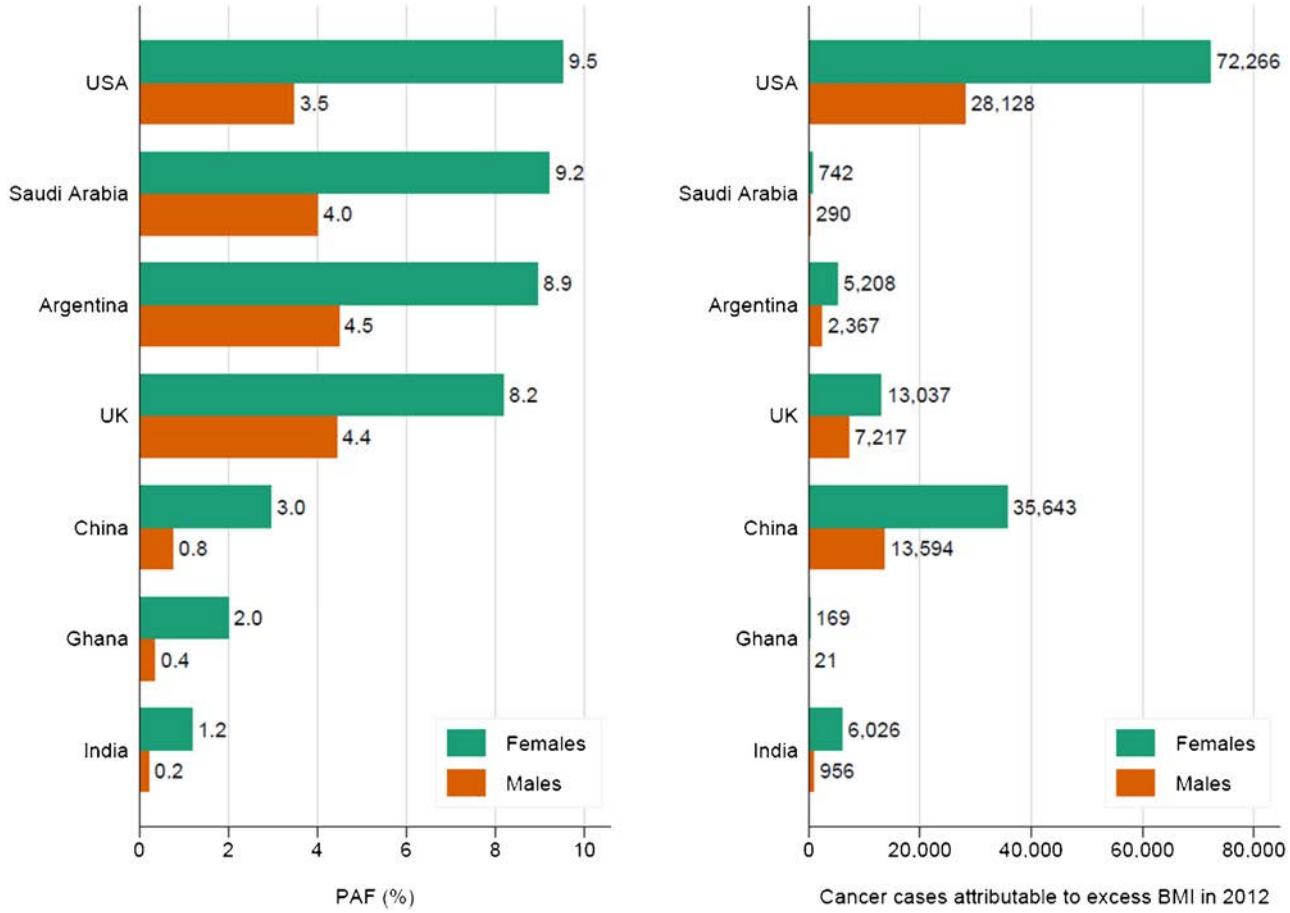

Fig. 3. Population attributable fraction (PAF, % left panel) and number of cancer cases (right panel) due to high body mass index in selected countries from various global regions in 2012 [15].

fat distribution or more precisely of the body girth at the level of the abdomen indicating abdominal fat mass [37]. Both WC and BMI are strongly correlated with general adiposity [38], and are also highly inter-correlated [30], but WC has shown to be a better predictor of intra-abdominal or visceral adipose tissue (VAT) than BMI in both sexes [38]. Excess VAT is associated with elevated IL-6, free fatty acids and TNF-α and is related to reduced levels of adiponectin [39]. These factors are associated with systemic inflammation, insulin resistance and the activation of the insulin-like growth factor (IGF) system, leading to a pro-tumorigenic microenvironment that promotes the development of cancer at the cellular level [40]. VAT may then be more relevant to cancer development than general adiposity [40]. Certain ethnicities differ in their susceptibility to visceral fat accumulation for a given amount of total body fat [41], which offers an alternative explanation as to why cancer risk differs across ethnic groups [42]. The gold standard for measurement of VAT, such as magnetic resonance imaging (MRI) and computed tomography, is quite costly [43]. It is therefore not surprising that studies utilizing VAT have been historically of small size, of cross-sectional or case-control design, and with intermediate cancer endpoints [44], until recently [45]. Another measurement based on dual-energy X-ray absorptiometry (DXA) has emerged as a more affordable option [46], and may yet prove a valuable assessment of body composition in ethnically-varied populations, although DXA does not allow separating abdominal body fat into subcutaneous and VAT. Nevertheless, a recent dose-response meta-analysis of six observational studies supported the hypothesis that VAT may be the underlying mediator of the observed association of BMI and WC with colorectal adenomas [44].

Future studies using more accurate measures of adiposity and considering different body fat compartments will be important in assessing whether cancer risk is specific to VAT or whether VAT more appropriately represents a marker of subcutaneous fat dysfunction leading to metabolic disease and cancer [47]. The prospective cohort studies currently underway, including the UK Biobank [48] and the German National Cohort [49], are implementing imaging methods on a large scale, and thus will yield novel areas for future research on obesity and cancer research.

5. The importance of assessing lifetime obesity

While epidemiologic studies have quantified the importance of dose-response and cumulative lifetime exposure for risk factors such as smoking, equivalent appraisals of obesity are lacking, despite the evidence that dose and timing of obesity have an important impact on disease risk. Earlier and accumulated exposure to overweight have been found to increase the risk and severity of hypertension, insulin resistance, chronic inflammation, oxidative DNA damage and alterations in endogenous hormone metabolism—all key mechanisms on the obesity-cancer pathway [50–52]. To date, rather few studies have investigated the relationship between obesity and cancer from a life course perspective, probably due to a lack of prospective data on repeated

anthropometric measurements over a long duration of follow-up. While these are necessary to capture the full continuum of lifetime overweight exposure and to quantify corresponding health effects, recent studies support the hypothesis that the association between excess weight and cancer risk and mortality compounds with time [53,54].

In a recent study from the Women's Health Initiative among postmenopausal women, every ten-year increase in adulthood overweight duration was associated with a 5% increase in the risk of breast cancer and a 17% increase in endometrial cancer [55]. On adjusting for intensity of overweight (a measure not dissimilar to pack-years of cigarette smoking), these figures rose to 8% and 37%, respectively. Similarly, in a recent study on lifetime adiposity and pancreatic cancer, a hazard ratio of 1.06 (95% CI: 1.02–1.09) was reported for each 10-year increment in overweight duration, with risks being even more pronounced (HR = 1.18, 95% CI: 1.05–1.32) in diabetics [54]. Age-dependent and cumulative effects of weight change have previously been reported to affect the risk of postmenopausal breast cancer, suggesting that weight gain during adult life, especially after the menopause, increases the risk of postmenopausal breast cancer [56–58]. In contrast, weight loss after menopause has been found to lead to a risk reduction [57]. It has also been shown that adult weight gain from ages 20 to 50 was associated a 60% greater risk of colon cancer [59], whereas weight gain or loss later in life was not related to colon cancer risk [60]. Weight gain over the life course has also been related to an increased risk of breast cancer in Hispanic women [61].

Other important questions concern obesity in early life and age at obesity onset in relation to cancer outcomes. Similar to the trends seen in adults, the prevalence of overweight and obesity has also been steeply rising in children and adolescents, with 23.8% of boys and 22.6% of girls in developed countries, and 12.9% of boys and 13.4% of girls in developing countries being overweight or obese in 2013 [62]. In a recent meta-analysis by Genkinger et al. using pooled data from 20 cohort studies, obesity during early adulthood (ages 18–21 years) had a stronger influence on pancreatic cancer mortality than obesity arising in later adulthood [63]. Similarly, childhood obesity has been associated with an increased risk of oesophageal adenocarcinoma many decades later in life [64]. Yet, childhood obesity has also been linked to a decreased risk of breast cancer [65], meaning that the role of obesity at different stages of the maturation process still needs to be explored. As obesity during childhood and early adulthood was still relatively uncommon in today's generation that is relevant for cancer research, but has been rising dramatically in the past 20 years [62], the full consequences of this development will only be visible in several decades.

In view of the ongoing and aggravating obesity epidemic worldwide, insights into the relation between cumulative overweight exposure and cancer development have become vital for the planning and implementation of effective prevention strategies and policies. For high income countries, where the prevalence of high BMI has been increasing for a few decades, a reduction in the mean BMI at the population level would still likely have a positive impact in reducing the national burden of cancers linked to obesity. In many countries however, further increases in the obesity-related cancer burden are anticipated given the latest trends in childhood obesity and the lag time until cancer development. Actions to keep overweight and obesity at a low level should become a key target in public health policy in countries that have not yet been touched by the obesity epidemic. At the global level, comprehensive and multi-faceted prevention approaches are fundamental to supporting individuals making healthier lifestyle choice and reducing and/or preventing obesity [31].

6. The impact of high body mass index on cancer outcomes

Given the volume of epidemiological evidence linking excess adiposity with increased incidence of several adult cancer types, and the plausible biological mechanisms underpinning these associations [42], it is reasonable to speculate that excess weight also has an adverse effect on patients who develop 'obesity-related' cancers. Indeed, there are several systematic reviews and meta-analyses of studies in this setting that support this hypothesis. For example, patients with colorectal cancer and with excess body weight are reported to have a 22% higher colorectal cancer-specific and 25% higher all-cause mortality relative to patients with normal weight [66]. Similar hazards are observed for breast cancer patients who were obese before diagnosis (40% decreased survival [67] and for patients with pancreatic cancer (53% decreased survival for BMI $\geq$35 kg/m^2 compared with those with BMI $<$25 kg/m^2 [68]. However, interpretation of these data is not straightforward and whether or not these associations are causal, is far from clear. It is important to establish causality (or not) here, as these studies inform some of the rationale for clinical guidelines on weight management among cancer survivors [20].

In the setting of excess weight and increased cancer incidence, associations are consistent, generally observed over a plausible timeframe (greater than 8 years, [24] and demonstrate specificity for gender (for example, men > women for colon cancer [24] and anatomic site (colon > rectum [24]. In the setting of cancer-related mortality and survival, these attributes of Bradford-Hill causality are generally lacking.

Furthermore, and importantly, the recent literature has recognized that many of the inconsistencies of associations in this setting are due to when BMI, or other anthropometric indicators, were measured. The World Cancer Research Fund (WCRF) [69] report on breast cancer survivorship highlighted this, and identified three broad categories of studies based on when the anthropometric measure was recorded—pre-diagnosis (or cohort inception), as a surrogate of 'usual body weight'; peri-diagnosis; and post-diagnosis (typically 12 months after diagnosis), the latter as a surrogate for 'body weight during survivorship'. When viewed in this manner, the patterns of association differ. In general, there are associations between pre-diagnosis BMI and cancer-related mortality, which in part are conditional on the association between excess body weight and incidence cancer. By contrast, associations between peri-diagnosis BMI and survivorship BMI, and survival are less consistent, and to interpret these requires inclusion of key prognostic factors (stage, treatment, and performance status) in patients with cancer. Similar patterns have been observed for colorectal cancer when classified by when the anthropometric indicator was measured [70].

There are a number of specific issues worth discussing in relation to body weight, cancer diagnosis and outcome. First, for the most part, the methodology used to test this relationship is prognostic modelling—and this requires inclusion of key prognostic factors (other than excess body weight). For most cancers of interest, these are stage and treatment. In modern oncology practice, treatment is multi-dimensional and there can be multiple stages in the same patient group at different points in the treatment pathway. This is well-illustrated for rectal cancer. Pre-treatment MR imaging determines the cT stage; post-surgical pathology assessment defines the pT stage; and if the patient has received downstaging chemoradiotherapy, the post-surgical pathology assessment defines the ypT stage. Thus, there are three staging systems. Chemotherapy administered as part of pre-operative chemoradiotherapy differs in type of regimen and rationale to that used for adjuvant chemotherapy, and chemotherapy used in the setting of metastatic disease. Few large-scale

epidemiological datasets have this level of detail to account for these various prognostic determinants.

Second, is the prognostic factor performance status and occurrence of co-morbidities. For example, in breast cancer, part of the observed reduction in survival has been related to comorbid conditions that are more common in cancer patients who are obese as compared to those who are normal weight (60% vs. 25%, respectively) [71]. The 'clustering' of risk factors for mortality [72] require investigators to consider survival biases and whether or not to account for these in analyses (for example, competing risk analyses). Third, there is a need to interpret with caution studies that relate anthropometric measures with cancer-related prognostic factors, such as histological grade or other phenotypes, such as receptor sub-types in breast cancer [73]. These cancer subtypes themselves trigger specific treatment pathways, such that the interpretation becomes confounded by treatment indication. Fourth, there is an increasing need to classify cancers (such as breast, colorectal and prostate) based on screen-detected or not. This level of detail is seldom available in large-scale analyses. Patients with screen-detected cancers frequently have a better outcome, stage for stage, compared with non-screen detected. And the presence of obesity itself can influence participation in cancer-screening. Fifth, there is an increasing recognition that race and ethnicity might be relevant to the evaluation of BMI and cancer survival. In ethnically distinct populations, it is speculated that differences in the distribution of other risk factors and co-morbidities may be responsible for different effects on mortality due to different competing causes of death [74]. Currently, the evidence for this is indirect, but if it were to turn out to be causal, this would have major implications for the explanations of variations in cancer-related mortality rates around the globe [14]. Yet, the role of genetic ancestry and its relation with cancer survivorship also remains to be explored in the future.

Additionally, it is increasingly recognized that rather than obesity predicting for an adverse cancer prognosis, being overweight (BMI: 25.0–29.9 kg/m^2) and obese I category (BMI: 30.0–34.9 kg/m^2) are associated with an improved survival compared with normal weight. This is known as the 'obesity paradox'. Apart from possible biological explanations (implausibility of single 'ideal weight' (for height) concept, advantages of higher weight in aging through a number of mechanisms such as a favorable lipid profile and reduction in the impact of oxidative stress and inflammation [75]), there are a number of plausible methodological reasons to explain this—such as residual confounding, reverse causality, and a specific type of selection bias known as 'collider bias'. The latter bias refers to an exaggerated effect of a confounder (e.g. smoking) that results from stratifying by disease status and may lead to obesity appearing protective [76]. This is an area of active research and is not yet conclusive. The reader certainly should not interpret these observations as a rationale to recommend that high BMI to reduce risk of death among cancer patients.

Finally, in view of the increasing number of long-term cancer survivors [77,78], partly caused by earlier cancer detection and improved cancer treatment, obesity has also to become a major prevention target beyond the first primary cancer diagnosis. The growing body of survivorship research suggests that higher BMI is not only entailing poorer outcomes in terms of occurrence of cancer-specific recurrence or a second cancer, but also comorbidities, postsurgical wound healing and infection [79]. Guiding cancer survivors towards better lifestyle choices thereby favorably influencing survivorship trajectories is vital in this growing population group (for recommendations please refer to [80] that include maintaining healthy weight, and also other healthy lifestyle such as stopping smoking).

7. Future burden of obesity-related cancers: implications for prevention

In a previous paper, we have illustrated the potential for reducing obesity-related cancers through a realistically attainable goal that assumes no change in BMI over three decades. We recalculated the preventable fraction of cancer related to excess weight using historical BMI levels (national mean BMI in 1982). In total, 0.4% of all cancers in males and 1.1% in females in 2012 could have been prevented if populations had maintained their BMI over the past decades [15]. Aggregated, this represents about one fourth (or 104,501) of all cancers attributable to excess BMI in 2012. Of particular relevance to the estimation of the number of cancers attributable to obesity is whether actions that stabilize the current obesity epidemic will be sufficient in reducing the future burden of obesity-related cancers, or whether obesity trends need to be reversed in order to return to rates of obesity-related cancers observed today. Of note, younger generations are experiencing a greater prevalence of obesity and are projected to carry a longer duration of obesity for a given age relative to previous generations [81]. This warrants additional research on the expected effects of these trends on the future incidence of obesity-related cancers.

Considering the global significance of the impact of obesity on cancer, little effort has been undertaken globally to create the data infrastructure necessary to monitor the BMI distribution and its changes over time across populations. An additional challenge is the linkage of these data with other databases on distal and environmental determinants that affect obesity [82]. Great challenges remain in reducing individual BMI, yet a number of intervention trials have demonstrated some successes over 12–18 months periods, such as the effectiveness of physical activity and diet programs implemented in clinical practices or regular dietician visits [83–86]. In addition, there is a need to develop a range of comprehensive, large-scale public health policies aimed at improving energy imbalance in order to curb the obesity epidemic [87]. Indeed, successful prevention programmes require a tailored approach taking into account local political and economic systems, local knowledge of food supply systems and also the sociocultural, socioeconomic, recreation and transport environment [82,88]. If left unchecked, the adverse consequences of the obesity epidemic threaten the progress that has been made in the prevention of other risk factors such as smoking, making it the number one modifiable lifestyle risk factor, responsible for the increasing burden of a whole range of non-communicable diseases.

Authorship contribution

This is to confirmed that each author listed above has contributed to the paper as recommended by the International Committee of Medical Journal Editors "Uniform requirements for manuscripts submitted to biomedical journals". All have substantially contributed to conception and design, acquisition of data, or analysis and interpretation of data and has contributed in drafting the article and/or critically revising. All have as well given the final approval of the version to be submitted and published.

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References

[1] G.A. Stevens, G.M. Singh, Y. Lu, G. Danaei, J.K. Lin, M.M. Finucane, et al., National, regional, and global trends in adult overweight and obesity prevalences, Popul. Health Metrics 10 (1) (2012) 22.

[2] G.M. Singh, G. Danaei, F. Farzadfar, G.A. Stevens, M. Woodward, D. Wormser, et al., The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis, PLoS One 8 (7) (2013) e65174.

[3] Food nutrition, physical activity and the prevention of cancer: a global perspective: a project of World Cancer Research Fund International. American Institute for Cancer Research. World Cancer Research Fund, Washington, D.C. (2007). xxv, 517 pp.

[4] C. Prospective Studies, G. Whitlock, S. Lewington, P. Sherliker, R. Clarke, J. Emberson, et al., Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies, Lancet 373 (9669) (2009) 1083–1096.

[5] G.B.D.R.F. Collaborators, M.H. Forouzanfar, L. Alexander, H.R. Anderson, V.F. Bachman, S. Biryukov, et al., Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013, Lancet (2015) .

[6] Food Nutrition, Physical activity, and the Prevention of Breast Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2010).

[7] Food Nutrition, Physical activity, and the Prevention of Colorectal Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2011).

[8] Food Nutrition, Physical activity, and the Prevention of Pancreatic Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2012).

[9] Food Nutrition, Physical activity, and the Prevention of Endometrial Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2013).

[10] Food Nutrition, Physical activity, and the Prevention of Ovarian Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2014).

[11] M.L. Cheng, L. Zhang, M. Borok, E. Chokunonga, C. Dzamamala, A. Korir, et al., The incidence of oesophageal cancer in Eastern Africa: identification of a new geographic hot spot? Cancer Epidemiol. 39 (2) (2015) 143–149.

[12] N.I. Somdyala, D.M. Parkin, N. Sithole, D. Bradshaw, Trends in cancer incidence in rural Eastern Cape Province; South Africa, 1998–2012, Int. J. Cancer 136 (5) (2015) E470–E474.

[13] Diet Nutrition, Physical activity, and Liver Cancer. Continuous Update Project Report. World Cancer Research Fund/American Institute for Cancer Research (2015).

[14] GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer. (2013). Available from: http://globocan.iarc.fr.

[15] M. Arnold, N. Pandeya, G. Byrnes, A.G. Renehan, G.A. Stevens, M. Ezzati, et al., Global burden of cancer attributable to high body-mass index in 2012: a population-based study, Lancet Oncol. 16 (1) (2015) 36–46.

[16] F. Bray, A. Jemal, N. Grey, J. Ferlay, D. Forman, Global cancer transitions according to the Human Development Index (2008–2030): a population-based study, Lancet Oncol. 13 (8) (2012) 790–801.

[17] C. Hoyo, M.B. Cook, F. Kamangar, N.D. Freedman, D.C. Whiteman, L. Bernstein, et al., Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium, Int. J. Epidemiol. 41 (6) (2012) 1706–1718.

[18] S.S. Devesa, W.J. Blot, J.F. Fraumeni Jr., Changing patterns in the incidence of esophageal and gastric carcinoma in the United States, Cancer 83 (10) (1998) 2049–2053.

[19] M. Arnold, I. Soerjomataram, J. Ferlay, D. Forman, Global incidence of oesophageal cancer by histological subtype in 2012, Gut 64 (3) (2015) 381–387.

[20] J.A. Ligibel, C.M. Alfano, K.S. Courneya, W. Demark-Wahnefried, R.A. Burger, R. T. Chlebowski, et al., American society of clinical oncology position statement on obesity and cancer, J. Clin. Oncol. 32 (31) (2014) 3568–3574.

[21] A.R. Omran, The epidemiologic transition: a theory of the epidemiology of population change. 1971, Milbank Q. 83 (4) (2005) 731–757.

[22] J.M. Gaziano, Fifth phase of the epidemiologic transition: the age of obesity and inactivity, JAMA 303 (3) (2010) 275–276.

[23] M.M. Finucane, G.A. Stevens, M.J. Cowan, G. Danaei, J.K. Lin, C.J. Paciorek, et al., National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants, Lancet 377 (9765) (2011) 557–567.

[24] A.G. Renehan, M. Tyson, M. Egger, R.F. Heller, M. Zwahlen, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies, Lancet 371 (9612) (2008) 569–578.

[25] L.L. Moore, M.L. Bradlee, M.R. Singer, G.L. Splansky, M.H. Proctor, R.C. Ellison, et al., BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham study adults, Int. J. Obes. Relat. Metab. Disord. 28 (4) (2004) 559–567.

[26] I. Janssen, P.T. Katzmarzyk, R. Ross, Waist circumference and not body mass index explains obesity-related health risk, Am. J. Clin. Nutr. 79 (3) (2004) 379–384.

[27] G. Vazquez, S. Duval, D.R. Jacobs Jr., K. Silventoinen, Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis, Epidemiol. Rev. 29 (2007) 115–128.

[28] A. Amadou, P. Ferrari, R. Muwonge, A. Moskal, C. Biessy, I. Romieu, et al., Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis, Obes. Rev. (2013) .

[29] WHO Expert Consultation, Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies, Lancet 363 (9403) (2004) 157–163.

[30] F. Hu, Obesity Epidemiology, Oxford University Press, Oxford; New York, 2008 (xiii, 498 pp.).

[31] Obesity: preventing and managing the global epidemic. Report of a WHO consultation, World Health Organ. Tech. Rep. Ser. 894 (i–xii) (2000) 1–253.

[32] Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health, Obes. Res. 6 (Suppl. 2) (1998) 51S–209S.

[33] Y. Ning, L. Wang, E.L. Giovannucci, A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies, Obes. Rev. 11 (1) (2010) 19–30.

[34] M.A. Cornier, J.P. Despres, N. Davis, D.A. Grossniklaus, S. Klein, B. Lamarche, et al., Assessing adiposity: a scientific statement from the American Heart Association, Circulation 124 (18) (2011) 1996–2019.

[35] A.E. Locke, B. Kahali, S.I. Berndt, A.E. Justice, T.H. Pers, F.R. Day, et al., Genetic studies of body mass index yield new insights for obesity biology, Nature 518 (7538) (2015) 197–206.

[36] M.D. Fesinmeyer, K.E. North, M.D. Ritchie, U. Lim, N. Franceschini, L.R. Wilkens, et al., Genetic risk factors for BMI and obesity in an ethnically diverse population: results from the population architecture using genomics and epidemiology (PAGE) study, Obes. (Silver Spring) 21 (4) (2013) 835–846.

[37] S. Klein, D.B. Allison, S.B. Heymsfield, D.E. Kelley, R.L. Leibel, C. Nonas, et al., Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association, Diabetes Care 30 (6) (2007) 1647–1652.

[38] W. Shen, M. Punyanitya, Z. Wang, D. Gallagher, M.P. St-Onge, J. Albu, et al., Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image, J. Appl. Physiol. (1985) 97 (6) (2004) 2333–2338.

[39] M.P. Scheid, G. Sweeney, The role of adiponectin signaling in metabolic syndrome and cancer, Rev. Endocr. Metab. Disord. 15 (2) (2014) 157–167.

[40] C.L. Donohoe, S.L. Doyle, J.V. Reynolds, Visceral adiposity, insulin resistance and cancer risk, Diabetol. Metab. Syndr. 3 (2011) 12.

[41] J.P. Despres, I. Lemieux, Abdominal obesity and metabolic syndrome, Nature 444 (7121) (2006) 881–887.

[42] A.G. Renehan, M. Zwahlen, M. Egger, Adiposity and cancer risk: new mechanistic insights from epidemiology, Nat. Rev. Cancer 15 (8) (2015) 484–498.

[43] W. Shen, Z. Wang, M. Punyanita, J. Lei, A. Sinav, J.G. Kral, et al., Adipose tissue quantification by imaging methods: a proposed classification, Obes. Res. 11 (1) (2003) 5–16.

[44] N. Keum, D.H. Lee, R. Kim, D.C. Greenwood, E.L. Giovannucci, Visceral adiposity and colorectal adenomas: dose-response meta-analysis of observational studies, Ann. Oncol. 26 (6) (2015) 1101–1109.

[45] R.A. Murphy, T.F. Bureyko, I. Miljkovic, J.A. Cauley, S. Satterfield, T.F. Hue, et al., Association of total adiposity and computed tomographic measures of regional adiposity with incident cancer risk: a prospective population-based study of older adults, Appl. Physiol. Nutr. Metab. 39 (6) (2014) 687–692.

[46] M.P. Rothney, R.J. Brychta, E.V. Schaefer, K.Y. Chen, M.C. Skarulis, body composition measured by dual-energy X-ray absorptiometry half-body scans in obese adults, Obesity 17 (6) (2009) 1281–1286.

[47] T. Tchkonia, T. Thomou, Y. Zhu, I. Karagiannides, C. Pothoulakis, M.D. Jensen, et al., Mechanisms and metabolic implications of regional differences among fat depots, Cell Metab. 17 (5) (2013) 644–656.

[48] S.E. Petersen, P.M. Matthews, F. Bamberg, D.A. Bluemke, J.M. Francis, M.G. Friedrich, et al., Imaging in population science: cardiovascular magnetic resonance in 100,000 participants of UK Biobank—rationale, challenges and approaches, J. Cardiovasc. Magn. Reson. 15 (2013) 46.

[49] German National Cohort C, The German National Cohort: aims, study design and organization, Eur. J. Epidemiol. 29 (5) (2014) 371–382.

[50] F. Bianchini, R. Kaaks, H. Vainio, Overweight, obesity, and cancer risk, Lancet Oncol. 3 (9) (2002) 565–574.

[51] A. Abdullah, F.A. Amin, J. Stoelwinder, S.K. Tanamas, R. Wolfe, J. Barendregt, et al., Estimating the risk of cardiovascular disease using an obese-years metric, BMJ Open 4 (9) (2014) e005629.

[52] A. Abdullah, J. Stoelwinder, S. Shortreed, R. Wolfe, C. Stevenson, H. Walls, et al., The duration of obesity and the risk of type 2 diabetes, Public Health Nutr. 14 (1) (2011) 119–126.

[53] A. Abdullah, R. Wolfe, J.U. Stoelwinder, M. de Courten, C. Stevenson, H.L. Walls, et al., The number of years lived with obesity and the risk of all-cause and cause-specific mortality, Int. J. Epidemiol. 40 (4) (2011) 985–996.

[54] R.Z. Stolzenberg-Solomon, C. Schairer, S. Moore, A. Hollenbeck, D.T. Silverman, Lifetime adiposity and risk of pancreatic cancer in the NIH-AARP Diet and Health study cohort, Am. J. Clin. Nutr. 98 (4) (2013) 1057–1065.

[55] Arnold M., Jiang L., Stefanick M.L., Johnson K.C., Lane D.S., LeBlanc E.S., et al. Adulthood overweight, obesity, and cancer risk in the Women's Health Initiative: potential for prevention. submitted.

[56] J. Ahn, A. Schatzkin, J.V. Lacey Jr., D. Albanes, R. Ballard-Barbash, K.F. Adams, et al., Adiposity, adult weight change, and postmenopausal breast cancer risk, Arch. Intern. Med. 167 (19) (2007) 2091–2102.
[57] A.H. Eliassen, G.A. Colditz, B. Rosner, W.C. Willett, S.E. Hankinson, Adult weight change and risk of postmenopausal breast cancer, JAMA 296 (2) (2006) 193–201.
[58] K. Krishnan, J.K. Bassett, R.J. MacInnis, D.R. English, J.L. Hopper, C. McLean, et al., Associations between weight in early adulthood, change in weight, and breast cancer risk in postmenopausal women, Cancer Epidemiol. Biomarkers Prev. 22 (8) (2013) 1409–1416.
[59] K. Aleksandrova, T. Pischon, B. Buijsse, A.M. May, P.H. Peeters, H.B. Bueno-de-Mesquita, et al., Adult weight change and risk of colorectal cancer in the European prospective investigation into cancer and nutrition, Eur. J. Cancer 49 (16) (2013) 3526–3536.
[60] C.N. Steins Bisschop, C.H. van Gils, M.J. Emaus, H.B. Bueno-de-Mesquita, E.M. Monninkhof, H. Boeing, et al., Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study, Am. J. Clin. Nutr. 99 (1) (2014) 139–147.
[61] A. Amadou, G. Torres Mejia, G. Fagherazzi, C. Ortega, A. Angeles-Llerenas, V. Chajes, et al., Anthropometry, silhouette trajectory, and risk of breast cancer in Mexican women, Am. J. Prev. Med. 46 (3) (2014) S52–S64.
[62] M. Ng, T. Fleming, M. Robinson, B. Thomson, N. Graetz, C. Margono, et al., Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet (2014) .
[63] J.M. Genkinger, C.M. Kitahara, L. Bernstein, A. Berrington de Gonzalez, M. Brotzman, J.W. Elena, et al., Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies, Ann. Oncol. (2015) .
[64] M.B. Cook, N.D. Freedman, M. Gamborg, T.I. Sorensen, J.L. Baker, Childhood body mass index in relation to future risk of oesophageal adenocarcinoma, Br. J. Cancer 112 (3) (2015) 601–607.
[65] H.J. Baer, S.S. Tworoger, S.E. Hankinson, W.C. Willett, Body fatness at young ages and risk of breast cancer throughout life, Am. J. Epidemiol. 171 (11) (2010) 1183–1194.
[66] J. Lee, J.A. Meyerhardt, E. Giovannucci, J.Y. Jeon, Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies, PLoS One 10 (3) (2015) e0120706.
[67] D.S. Chan, A.R. Vieira, D. Aune, E.V. Bandera, D.C. Greenwood, A. McTiernan, et al., Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies, Ann. Oncol. 25 (10) (2014) 1901–1914.
[68] C. Yuan, Y. Bao, C. Wu, P. Kraft, S. Ogino, K. Ng, et al., Prediagnostic body mass index and pancreatic cancer survival, J. Clin. Oncol. 31 (33) (2013) 4229–4234.
[69] World Cancer Research Fund International. Continuous Update Project Report: Diet, Nutrition, Physical Activity, and Breast Cancer Survivors, 2014. Available at: www.wcrf.org/sites/default/files/Breast-Cancer-Survivors-2014-Report.pdf (accessed 20.12.14)
[70] E. Parkin, D.A. O'Reilly, D.J. Sherlock, P. Manoharan, A.G. Renehan, Excess adiposity and survival in patients with colorectal cancer: a systematic review, Obes. Rev. 15 (5) (2014) 434–451.
[71] M.L. Kwan, W.Y. Chen, C.H. Kroenke, E.K. Weltzien, J.M. Beasley, S.J. Nechuta, et al., Pre-diagnosis body mass index and survival after breast cancer in the after breast cancer pooling project, Breast Cancer Res. Treat. 132 (2) (2012) 729–739.
[72] I. Soerjomataram, M.S. Thong, I.J. Korfage, S. Polinder, A. van der Heide, E. de Vries, et al., Excess weight among colorectal cancer survivors: target for intervention, J. Gastroenterol. 47 (9) (2012) 999–1005.
[73] R. Suzuki, N. Orsini, S. Saji, T.J. Key, A. Wolk, Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis, Int. J. Cancer 124 (3) (2009) 698–712.
[74] K.H. Schmitz, M.L. Neuhouser, T. Agurs-Collins, K.A. Zanetti, L. Cadmus-Bertram, L.T. Dean, et al., Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity, J. Natl. Cancer Inst. 105 (18) (2013) 1344–1354.
[75] J.B. Dixon, G.J. Egger, E.A. Finkelstein, J.G. Kral, G.W. Lambert, 'Obesity paradox' misunderstands the biology of optimal weight throughout the life cycle, Int. J. Obes. (Lond.) 39 (1) (2015) 82–84.
[76] H.R. Banack, J.S. Kaufman, From bad to worse: collider stratification amplifies confounding bias in the obesity paradox, Eur. J. Epidemiol. 30 (10) (2015) 1111–1114.
[77] J.S. de Moor, A.B. Mariotto, C. Parry, C.M. Alfano, L. Padgett, E.E. Kent, et al., Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care, Cancer Epidemiol. Biomarkers Prev. 22 (4) (2013) 561–570.
[78] G. Gatta, S. Mallone, J.M. van der Zwan, A. Trama, S. Siesling, R. Capocaccia, et al., Cancer prevalence estimates in Europe at the beginning of 2000, Ann. Oncol. 24 (6) (2013) 1660–1666.
[79] W. Demark-Wahnefried, E.A. Platz, J.A. Ligibel, C.K. Blair, K.S. Courneya, J.A. Meyerhardt, et al., The role of obesity in cancer survival and recurrence, Cancer Epidemiol. Biomarkers Prev. 21 (8) (2012) 1244–1259.
[80] C.L. Rock, C. Doyle, W. Demark-Wahnefried, J. Meyerhardt, K.S. Courneya, A.L. Schwartz, et al., Nutrition and physical activity guidelines for cancer survivors, CA Cancer J. Clin. 62 (4) (2012) 243–274.
[81] J.M. Lee, S. Pilli, A. Gebremariam, C.C. Keirns, M.M. Davis, S. Vijan, et al., Getting heavier, younger: trajectories of obesity over the life course, Int. J. Obes. (Lond.) 34 (4) (2010) 614–623.
[82] B.A. Swinburn, G. Sacks, K.D. Hall, K. McPherson, D.T. Finegood, M.L. Moodie, et al., The global obesity pandemic: shaped by global drivers and local environments, Lancet 378 (9793) (2011) 804–814.
[83] R.S. Bhopal, A. Douglas, S. Wallia, J.F. Forbes, M.E. Lean, J.M. Gill, et al., Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: a family-cluster randomised controlled trial, Lancet Diabetes Endocrinol. 2 (3) (2014) 218–227.
[84] M.L. Fitzgibbon, M.R. Stolley, L. Schiffer, L.K. Sharp, V. Singh, A. Dyer, Obesity reduction black intervention trial (ORBIT): 18-month results, Obes. (Silver Spring) 18 (12) (2010) 2317–2325.
[85] J. Hartmann-Boyce, D.J. Johns, S.A. Jebb, P. Aveyard, Behavioural weight management review G. Effect of behavioural techniques and delivery mode on effectiveness of weight management: systematic review, meta-analysis and meta-regression, Obes. Rev. 15 (7) (2014) 598–609.
[86] R. Ross, M. Lam, S.N. Blair, T.S. Church, M. Godwin, S.B. Hotz, et al., Trial of prevention and reduction of obesity through active living in clinical settings: a randomized controlled trial, Arch. Intern. Med. 172 (5) (2012) 414–424.
[87] B.M. Popkin, Global nutrition dynamics: the world is shifting rapidly toward a diet linked with noncommunicable diseases, Am. J. Clin. Nutr. 84 (2) (2006) 289–298.
[88] B.M. Popkin, What can public health nutritionists do to curb the epidemic of nutrition-related noncommunicable disease? Nutr. Rev. 67 (Suppl. 1) (2009) S79–S82.