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Cancer survivorship, excess body fatness and weight-loss intervention—where are we in 2020?

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1 **Cancer survivorship, excess body fatness and weight loss intervention — where are**
2 **we in 2020?**

3

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90 **On behalf of the UK NIHR Cancer and Nutrition Collaboration (Population Health**
91 **Stream)**

92 The Population Health Stream exists to promote research on key nutrition related factors in
93 the primary and secondary prevention of cancer. These are; diet and nutrition, alcohol,
94 physical activity and obesity. In calling for more research, the group is addressing an urgent
95 need for more effective cancer prevention strategies and interventions. We do not assign any
96 judgement or stigma to any groups or individuals on the basis of their lifestyle.

97

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111 **Abstract**

112 Earlier diagnosis and more effective treatments mean that the estimated number of cancer
113 survivors in the UK is expected to reach 4 million by 2030. However, there is an increasing
114 realisation that excess body fatness (EBF) is likely to influence the quality of cancer
115 survivorship and disease-free survival. For decades, the discussion of weight management
116 in patients with cancer has been dominated by concerns about unintentional weight loss, low
117 body weight and interventions to increase weight, often re-enforced by the existence of the
118 obesity paradox, which indicates that high body weight is associated with survival benefits
119 for some types of cancer. However, observational evidence provides strong grounds for
120 testing the hypothesis that interventions for promoting intentional loss of body fat and
121 maintaining skeletal muscle in overweight and obese cancer survivors would bring important
122 health benefits in terms of survival outcomes and long-term impact on treatment-related side
123 effects. In this article, we outline the need for studies to improve our understanding of the
124 health benefits of weight loss interventions, such as hypocaloric healthy eating plans
125 combined with physical activity. In particular, complex intervention trials that are
126 pragmatically designed are urgently needed to develop effective, clinically practical,
127 evidence-based strategies for reducing EBF and optimising body composition in people
128 living with and beyond common cancers.

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136 **Introduction**

137 Improvements in the early detection and treatment of cancer have led to a dramatic increase
138 in the number of cancer survivors — those people alive who have been diagnosed with
139 cancer before, during and after treatment¹. Globally, public health surveillance data show
140 that 5-year net survival rates from colon, rectal and breast cancers have increased steadily
141 in the majority of developed countries,² and, in the UK, the number of cancer survivors is
142 expected to reach 4 million by 2030³. The definition of survivors includes individuals who
143 have been cured by treatments or who are on the road to recovery and aiming to reduce the
144 risk of recurrence, as well as those living with metastatic disease, for whom efforts are more
145 focussed on maximising treatment effectiveness, managing the side-effects of treatment and
146 preserving quality of life.

147 As we celebrate extended cancer survivorship, however, we must also be mindful of co-
148 morbid conditions⁴, including overweight and obesity characterised by excess body fatness
149 (EBF), that can affect the quality of those additional years. Body mass index (BMI) is the
150 measure most commonly used as a proxy for EBF; the measure becomes notable when the
151 value increases beyond 25 kg/m² (overweight) and is deemed substantial at levels above
152 30kg/m² (obesity). It is estimated that, worldwide, 1.9 billion adults and over 340 million
153 children and adolescents are now living with overweight or obesity⁵. Although EBF has been
154 identified as a risk factor for at least 13 different types of cancer⁶, its effect on cancer
155 survivorship is less clear. However, the prevalence of EBF in Western societies means that
156 its probable influence on the quality of cancer survivorship and the prospect of prolonged
157 disease-free survival after primary curative treatment cannot be ignored. The effects of EBF
158 on insulin resistance, systemic inflammation and other circulating factors such as adipokines
159 and sex hormones, which are linked to primary cancer risk, are well described⁶, and
160 research into the biological mechanisms that underlie the obesity–cancer relationship (both
161 in tumour initiation and progression) is ongoing⁷. EBF can influence the quantity, distribution
162 and quality of adipose tissue, which is now recognised to comprise not just adipocytes, but

163 also blood vessel stromal cells and immune cells. Accordingly, the roles of adipose tissue
164 have been found to extend beyond triacylglycerol storage to include (among many others)
165 glucose and lipid metabolism, appetite regulation and, notably, immunity and inflammation,
166 providing potential mechanisms by which EBF might influence cancer survivorship and
167 response to treatment, as well as risk^{8,9}.

168

169 Several leading health authorities recommend the management of excess weight (e.g.
170 avoiding weight gain, intentional weight loss and weight loss maintenance) for people living
171 with and beyond cancer^{10,11,12} but service provision and resources for health behaviour
172 change and the promotion of effective interventions within healthcare systems is
173 suboptimal¹³. Weight management in cancer patients has routinely been dominated by
174 concerns about unintentional weight loss (secondary to cancer treatments or due to
175 progressive disease) and low body weight. These concerns have resulted in an emphasis on
176 nutritional interventions to maintain or increase weight because of the negative outcomes
177 associated with loss of body mass in people with advanced cancer. Nutrition screening tools
178 focus on parameters of under-nutrition with little heed to the issues and adverse risk profile
179 of patients who have EBF at diagnosis, or who gain further weight (body fat) during
180 treatment and beyond.

181 Consideration of the health benefits of managing EBF are largely overlooked. There is a
182 perception that many clinicians fail to be convinced that interventions related to EBF are a
183 key part of cancer care and will be beneficial to patient outcomes¹³. Clinicians might even
184 avoid these issues because they are concerned about evoking feelings of guilt or
185 undermining patient–health-professional relationships (especially where BMI is a known risk
186 factor for the cancer site),^{13,14} despite opportunities ('teachable moments') to address this
187 issue during and after cancer treatment.

188

189 The influence of intentional weight loss on adipose tissue biology is unknown. It is possible
190 that some effects of obesity might be imprinted, and therefore might not be reversible⁷. On
191 the other hand, work in mouse models suggests that intentional weight loss through caloric
192 restriction boosts anti-cancer immune surveillance and delays progression⁸. It is also
193 possible that these biological responses could enhance treatment outcomes and risk of
194 disease recurrence. The importance of understanding more about the impact of obesity on
195 both cancer incidence and outcomes was identified in 2020 as one of the eight research
196 priority areas needed to accelerate progress in cancer management by the American
197 Society for Clinical Oncology¹⁵. In this article, we outline the need for intervention trials to
198 address the issue of whether promoting intentional loss of body fat and maintaining skeletal
199 muscle in overweight and obese cancer survivors would bring important health benefits in
200 terms of survival outcomes and long-term impact on treatment-related side effects.
201 Realistically, management of excess body fatness is unlikely to become a core part of
202 survivorship plans unless robust clinical trials and subsequent clinical guidelines can be
203 developed.

204

205 **EBF and cancer survival**

206 Growing evidence from epidemiology studies indicates that avoiding EBF might have a role
207 in reducing cancer morbidity and mortality worldwide. The Global Burden of Disease Study
208 reported (using various ecological assumptions) in 2019 that amongst 896,040 colorectal
209 cancer deaths occurring in 2017, 73,475 (8.2%) were attributable to a high BMI¹⁶. A meta-
210 analysis of 82 studies reported a 35% increase in breast-cancer-related mortality and a 41%
211 increase in all-cause mortality in women with breast cancer who were obese, independent of
212 menopausal status¹⁷. Similarly, meta-analyses suggest that obesity is associated with poorer
213 survival outcomes in bladder,¹⁸ prostate,¹⁹ and hepatocellular²⁰ cancer patients.

214

215 ***The obesity paradox***

216 Considerable debate surrounds the ‘obesity paradox’^{21,22}, in which high body weight appears
217 to be associated with survival benefits after diagnosis of colorectal,²³ endometrial²⁴ and lung
218 cancer²⁵. In some studies, this phenomenon can be explained by the association of obesity
219 with less aggressive tumour subtypes, such as the increased incidence of type 1 tumours,
220 which have a good prognosis, compared with type 2 tumours, which have poor prognosis, in
221 obese endometrial cancer patients²⁶. A higher tolerance of some systemic anti-cancer
222 therapies in overweight/ obese patients and the benefit of energy reserves to support the
223 body during the stress of anti-cancer therapies have also been postulated as clinical
224 explanations for the obesity paradox (Figure 1). In some cases, higher body weight might
225 reflect greater fat free mass which may increase the responsiveness to treatment regimens²⁷
226 However, in many publications, the association of enhanced survival with overweight or
227 obese status is an artefact of methodological issues. These issues commonly include
228 combining cohorts of patients with early and advanced cancer so that observational data are
229 confounded by disease-related weight loss (reverse causality) and the use of heterogenous
230 cohorts that fail to adjust for tumour biology, stage or treatment, or other confounders such
231 as smoking. Other reported causes of the obesity paradox outlined in Figure 1 include
232 detection bias, where patients undergoing medical investigation for obesity-related co-
233 morbidities are diagnosed with incidental early-stage cancers, and collider bias, a specific
234 form of selection bias demonstrated in the relationships between smoking, cancer and
235 obesity. Cancer patients who are not obese might have other risk factors, such as smoking,
236 and an inverse association is therefore artificially strengthened between obesity and cancer
237 outcomes. Longer-term cohort studies that have the potential to provide better repeated
238 measures over time are needed. Finally, assessment of obesity by BMI fails to take body
239 composition, notably body fat distribution, into account. At the most basic measurement this
240 would include markers of central obesity such as waist circumference.

241

242 ***Weight gain after diagnosis and survival outcomes***

243 Data regarding weight gain after diagnosis of common cancers add another layer of
244 complexity to the link between EBF and cancer morbidity and mortality. For example,
245 whereas poorer survival outcomes associated with weight gain are suggested for breast
246 cancer after diagnosis²⁸, current evidence for the influence of weight gain after diagnosis on
247 colorectal cancer survival seems to be less clear-cut,²⁹ notably when patients with early
248 disease and those with metastatic disease (and high tumour burden) are included in the
249 same analysis. Although some studies suggest that a higher BMI might be associated with
250 better survival in patients with colorectal cancer, meta-analyses have reported little impact
251 on the risk of survivorship in overweight patients, whereas both obese and underweight
252 patients have an increased risk of all-cause mortality, cancer-specific mortality, disease
253 recurrence and worse disease-free survival compared with patients of normal weight³⁰. Being
254 able to distinguish between intentional and unintentional weight loss is also important, as is
255 the impact of weight loss on body composition — specifically, a reduction in EBF while
256 maintaining lean body mass is desirable. In addition, certain treatment modalities are
257 associated with weight gain, including endocrine therapy in breast and prostate cancer, and
258 steroid treatments used as an adjunct to many chemotherapy regimens and as supportive
259 care in many oncological emergencies associated with advanced cancer. These factors
260 highlight the importance of investigating EBF and weight gain by treatment. Added to this,
261 methodology concerns, including sampling selection bias, residual or unmeasured
262 confounding factors, reverse causation and collider bias, call into question the
263 epidemiological basis for the obesity paradox in this context.

264

265 ***EBF, skeletal muscle mass, surrogate measures and survivorship***

266 A growing number of observational studies have relied on surrogate measures of adiposity
267 (e.g. body weight, BMI, waist circumference), which do little to advance our understanding of
268 how changes in the key body composition parameters of EBF and skeletal muscle mass
269 might independently influence cancer survivorship. Caan *et al.*³¹ argued that people who are

270 overweight or obese generally have higher levels of skeletal muscle than people of lower
271 weight, thus decreasing the risk of disease recurrence, surgical complications and treatment-
272 related toxicities associated with lower skeletal muscle mass. It is, however, important to
273 analyse appropriately for age when classifying sarcopenia³². When age is taken into
274 consideration, sarcopenic obesity — skeletal muscle depletion despite high BMI — is
275 reported to be prevalent in approximately one-tenth of patients with advanced solid tumours
276 and is independently associated with increased complication and mortality rates across
277 multiple cancer sites and treatment plans³³. Furthermore, in non-metastatic breast cancer
278 patients, computer-tomography-derived measures of sarcopenia and total adiposity at
279 diagnosis were shown to be independently associated with overall mortality over six years of
280 follow-up, whereas BMI was not³⁴. These results further underline the need to assess body
281 composition rather than rely on BMI in order to guide best advice for nutritional and physical
282 activity survivorship plans.

283

284 **The effect of EBF on cancer treatment**

285 The effects of EBF and weight management interventions on treatment outcomes, post-
286 treatment morbidity and mortality might differ between cancer types, and many important
287 research questions in this arena need to be answered³⁵. For example, the impact of high BMI
288 (reflecting EBF) on the efficacy of local and systemic cancer therapies and associated side
289 effects in the context of optimising long-term treatment plans is largely understudied³⁶. A
290 systematic review of the effect of obesity on toxicity in women treated with chemotherapy in
291 early stage breast cancer concluded that obese patients tolerate chemotherapy better than
292 lean patients³⁷. However, it was acknowledged by the authors that this observation “may be
293 confounded by poorly specified dose-capping practices and the use of haematopoietic growth
294 factors” (which may have been used more frequently in obese patients if clinicians perceived
295 that these patients were at a higher risk of myelosuppression due to higher absolute drug
296 doses).

297 A narrative review³⁴ evaluating the effect of obesity on a wide variety of oncology treatment
298 modalities highlighted a number of points. First, technical challenges posed by high BMI
299 might adversely impact surgical morbidity outcomes (e.g. increased risk of surgical site
300 infections, reduced lymph node harvest and increased risk of margin positivity). Second, the
301 potential exists for suboptimal chemotherapy dosing; this is associated with capping
302 chemotherapy in obese patients to avoid toxicity and might be a driver of poor prognostic
303 outcomes. Conversely, however, the efficacy of immune checkpoint inhibition could
304 potentially be enhanced in patients who are obese . These checkpoints moderate the
305 immune response and the ability to impact on tumour cells. Immunotherapy agents have
306 been developed for a number of cancers and the importance of these in the overweight and
307 obese is emerging.³⁴

308

309 The review also raised an important question: does EBF influence outcomes directly through
310 cancer biology (such as via the effects of adipose tissue on the levels of oestrogens, insulin,
311 insulin-like growth factors and other adipokines to create a pro-inflammatory environment
312 that encourages carcinogenesis) or are the adverse outcomes of EBF mediated through
313 indirect pathways (e.g. chemotherapy dosing) that result in suboptimal treatment?

314

315 ***Interpreting the results of observational studies investigating the effect of EBF on***
316 ***mortality and survival***

317 Various studies have investigated the impact of EBF on a range of cancer outcomes in many
318 cancer types but, to date, the evidence on overall survivorship risks is inconclusive. In
319 summarising these studies (for example, in breast cancer), the World Cancer Research Fund
320 (WCRF) Continuous Update Project (CUP) panel¹⁰ developed a framework for interpreting the
321 effect of anthropometric measures on mortality and survival at three key time-points: pre-
322 diagnosis of cancer; peri-diagnosis/peri-treatment; and during survivorship (see Table 1).
323 Exposures (diet, physical activity, body composition) measured prior to cancer diagnosis are

324 anticipated to influence cancer incidence and overall mortality via an effect on cancer biology.
325 The main biological mechanisms of interest (metabolic regulators including insulin, insulin-like
326 growth factor 1, adipokines, inflammation-related molecules, and steroid hormones, as well
327 as the cellular and structural components of the tumour microenvironment, including adipose
328 tissue)³⁸ are likely to have long-term impacts without appropriate interventions.

329 Interventions based on these exposures are thus relevant to cancer prevention strategies
330 but further evidence will be required for weight management policies in cancer survivors.
331 Anthropometric measurements taken at the time of cancer diagnosis can be assessed as
332 prognostic indicators but must be interpreted in the context of the cancer type, stage and
333 patient performance status, as well as the timing of measurements in relation to treatment
334 modalities. The impact of body composition on therapy-related toxicities is equally important
335 in patients with advanced cancer where the goals of systemic therapies are to improve and
336 maintain quality of life whilst also extending life expectancy. This area is poorly addressed in
337 the current literature and represents an important unmet research need. However, as recent
338 weight loss is a frequent presentation of advanced stage cancer (reverse causality), there is
339 a need to analyse the association of body mass and survival in advanced stage patients
340 separately to that of patients with early stage disease who are less likely to present with
341 weight loss and will have a longer median survival time.

342 Assessment of body mass and size after treatment also needs attention in relation to the
343 type of treatment received for different tumour types and any associated toxicities, and an
344 awareness of selection against patients with rapid disease progression who have not
345 survived to this point.

346

347 ***Weight loss trials: a gap in the evidence***

348 Despite the limitations of observational data, the consistency and magnitude of associations
349 between EBF/weight gain and survival outcomes for some cancers reported in systematic

350 reviews and meta-analyses support the need for intervention studies^{27,39}. To date, weight
351 loss intervention studies have predominantly been carried out in breast cancer survivors. A
352 large-scale dietary intervention trial (low fat, high fruits and vegetables) in women with early-
353 stage breast cancer — the Women’s Intervention Nutrition Study (WINS) — was successful
354 in supporting women to lose weight, with indications of lower cancer recurrence in the
355 intervention group, notably in women with oestrogen-receptor (ER)-negative disease⁴⁰.
356 Furthermore, a growing number of short-term trials have demonstrated the effects of
357 intentional weight loss on blood-borne biomarkers of cancer and cardiometabolic risk,
358 including changes in serum sex hormones,⁴¹ inflammation markers⁴² and insulin sensitivity⁴³.
359 A small number of ongoing intentional weight loss trials are also ongoing in breast cancer
360 survivors^{44,45,46} and are expected to report on survival and associated outcomes over the
361 next decade. Weight loss trials have also been undertaken in endometrial cancer
362 survivors⁴⁷. However, a 2018 Cochrane review⁴⁸ concluded that there is insufficient high-
363 quality evidence to determine the effect of interventions on survival, quality of life or
364 cardiovascular events. The authors highlighted problems of high risk of bias by failing to
365 blind personnel and outcome assessors, and significant losses to follow-up. They also
366 emphasised the need for adequately powered trials with a follow-up of at least 5–10 years
367 duration.

368 Importantly, no trial has yet established the effect of intentional weight loss following a
369 cancer diagnosis on mortality and many gaps in our understanding of how to optimise such
370 interventions remain. The optimal contributions of diet composition, caloric intake, amount
371 and nature of physical activity (including sedentary time) for promoting loss of EBF and
372 avoiding weight gain⁴⁹ are important considerations for future intervention research.

373 Furthermore, the effects of weight management interventions on treatment-related side
374 effects, as well as bone health, physical function, psychosocial issues and quality of life,
375 have not been clearly defined for many cancers and intervention studies are needed to
376 address these important issues⁴⁸.

377 Weight management strategies in overweight and obese cancer survivors might also have a
378 role to play in the prevention of non-cancer deaths — for some individual patients, the
379 presence of EBF might also confer a poorer prognosis for survival from non-cancer disease.
380 For example, cancer patients who also have diabetes have a decreased overall survival
381 compared with cancer patients without diabetes, in part because they are at increased risk of
382 non-cancer (mainly cardiovascular) deaths,⁵⁰ which might be further increased by certain
383 treatments (e.g. anthracycline chemotherapy).

384 Whilst the case for examining the impact of weight management can be made from current
385 evidence, the design of programmes to capture the magnitude of effect and possible
386 negative consequences need to be fully explored.

387

388 **Time to invest in intervention research for EBF?**

389 Developing and testing interventions for promoting the intentional loss of EBF and
390 maintaining skeletal muscle mass require a number of considerations, which we outline
391 below.

392

393 ***Optimum timing of interventions***

394 The optimum window for weight loss interventions in cancer survivors needs careful
395 consideration. Treatment for cancer is increasingly being delivered over longer periods of
396 time and is multi-modal in nature; acute side effects, including unintentional gains in body
397 weight and changes in body composition, which might negatively influence cancer outcomes
398 and response to treatment, are not uncommon⁵¹. Of early-stage breast cancer patients
399 receiving chemotherapy, 30–60% gain significant weight. This weight gain involves losing
400 skeletal muscle while gaining adiposity⁵² and adversely impacts quality of life and overall
401 health⁵³. Young breast cancer patients can gain over 5% body weight in the first 12 months

402 after diagnosis⁵⁴, which is associated with changes in eating habits resulting from emotional
403 stress as well as the side effects of treatments (e.g. steroids and chemotherapy-induced
404 menopause, cancer-related fatigue and reduced physical activity). Clearly, interventions that
405 provide the support needed to help patients avoid or limit unintentional weight gain during
406 treatment and/or facilitate EBF loss following completion of treatment whilst maintaining
407 adequate levels of physical activity would be valuable adjuncts to curative cancer care
408 pathways.

409 Changes in nutritional and metabolic status that influence sarcopenia and cachexia must be
410 addressed with the appropriate nutritional support throughout treatment¹¹ irrespective of
411 body weight. For this reason, intentional weight loss interventions might be challenging and
412 possibly inadvisable for some cancer populations during the period of treatment, and the
413 post-treatment period is likely to offer a more practical time frame. For example,
414 chemoradiation treatment for patients with head and neck cancers is already associated with
415 a significant incidence of weight loss and malnutrition, and patients frequently require
416 nutritional support during treatment, while patients with upper gastrointestinal cancer often
417 present with rapid weight loss owing to dysphagia and, again, management should be
418 focussed on optimising nutritional intake prior to and during treatment.

419

420 ***The study population***

421 Careful consideration needs to be given to the study population, including age, location,
422 ethnicity, co-morbidities, primary cancer site and stage of disease when designing weight
423 loss interventions aimed at optimising efficacy and effectiveness. Trials to investigate the
424 benefits of intentional weight loss are most likely to be acceptable to clinicians and patients
425 in cancer populations where there is evidence that EBF is associated with second cancer
426 risk or poorer outcome. In addition, low frequency of rapid weight loss at presentation or
427 associated with common first-line treatment strategies will also make intentional weight loss

428 programmes seem more appropriate. Patients with early-stage presentations of breast,
429 endometrial, colorectal and prostate cancers might meet these requirements. Close attention
430 must also be paid to the biology of the disease, particularly within metastatic cancer
431 populations: patients with ER-positive metastatic breast cancer and no visceral disease
432 frequently have an indolent disease course that can be managed predominantly by
433 endocrine therapy over many years and constitute, potentially, a more appropriate
434 population for weight intervention strategies than patients with triple-negative metastatic
435 disease who frequently develop rapid disease progression leading to failure of vital organs.

436

437 ***Outcome measures***

438 Outcome measures in weight management trials should include those that are patient-
439 reported as well as clinically reported. Patient-reported outcomes (PROMS) include
440 measures of quality of life, which can be broadly categorised into five groups: general health
441 and well-being; physical factors (e.g. weight loss); symptoms (e.g. pain, nausea, fatigue);
442 psychological factors (e.g. anxiety, insomnia, self-esteem); and social factors (e.g.
443 relationships and work). Clinical outcome measures might vary according to cancer site and
444 treatment regimens, but should include those assessing acute and long-term side effects of
445 local and systemic therapies (e.g. lymphoedema volumes, fatigue scores, bone mineral
446 density, cardiac ejection fractions, etc.) as well as cancer outcomes (locoregional and distant
447 disease-free survival) and overall survival. Circulating biomarkers and surrogate endpoints
448 (e.g. adenomas, breast density,⁵⁵ etc.) should be used alongside PROMS to gain an
449 overview of relevant biological **and** well-being perspectives allowing clinical, scientific and
450 person-specific characteristics insights to the impact of interventions.

451

452 ***Minimising heterogeneity/standardising outcomes***

453 Sources of heterogeneity need to be carefully considered and controlled for in the design of
454 weight management studies and/or considered during the analytic phase. The potential for
455 clinical heterogeneity in outcomes exists according to disease subtype, stage and grade, as
456 well as in the treatment received, but methodological heterogeneity in the way outcomes are
457 defined can also occur. It is plausible that patients with different cancers might respond
458 differently to weight management interventions — notably, those with obesity-related
459 cancers versus non-obesity-related cancers. Standardising outcomes is important for
460 consistency and for comparison across trials and allows incorporation into meaningful meta-
461 analyses. To improve the definition and measurement of outcomes, the Core Outcome
462 Measures in Effectiveness Trials (COMET) initiative⁵⁶ provides guidance for researchers by
463 advocating a standardised set of outcomes that should be measured and reported, as a
464 minimum, in all clinical trials of health, including weight management. Examples listed in
465 Table 2 illustrate the breadth of outcomes, similarities and differences by site used by
466 different research teams and highlights the need for further work on agreed core
467 outcomes. Additionally, incorporation of the accumulating data to optimally predict obesity
468 treatment (ADOPT)⁵⁷ biological domain framework could advance the understanding of
469 individual variability in response to adult obesity treatments and explore the physiological
470 mechanisms that could influence cancer recurrence.

471

472 ***Weight management intervention design***

473 The design of weight management intervention (in terms of dose and duration) needs to be
474 driven by practicalities as well as the desired magnitude of change in body composition (e.g.
475 body fatness and skeletal muscle mass) — this approach has the greatest likelihood of
476 positively influencing patient and clinical outcomes⁵⁸. Caloric intake is the cornerstone of
477 weight loss, but regular physical activity and structured exercise programmes have important
478 roles to play in all aspects of weight management⁵⁹. Importantly, physical activity and
479 exercise can preserve skeletal muscle mass during dietary-induced fat loss^{60,61}, thereby

480 helping to protect against the adverse impact of sarcopenia on cancer survival outcomes^{31,62}
481 and increasing total daily energy output⁶³. Physical activity post-diagnosis is associated with
482 improved survival outcomes for patients with breast, colorectal or prostate cancer⁶⁴.
483 Furthermore, an international consensus statement concluded that sufficient evidence now
484 exists to show that regular exercise improves several cancer-related health outcomes,
485 including anxiety, depressive symptoms, fatigue, physical functioning and health-related
486 quality of life in cancer survivors⁶⁵.

487

488 The growing body of effective weight loss programmes (BRRIDE;⁶⁶ DIRECT;⁶⁷ DPP⁶⁸) that
489 have achieved clinically relevant changes (e.g. diabetes remission) in cancer and non-
490 cancer patients provides a good starting point for intervention design. However, translating
491 these programmes into cancer survivorship populations might require significant patient
492 involvement to ensure that the components (notably, dietary and structured exercise or
493 physical activity goals) can be achieved by those with a wide range of abilities, disabilities,
494 emotional needs, available time and financial circumstances. Furthermore, insights from
495 behavioural science⁶⁹ provide guidance for embedding strategies to support long-term
496 behavioural change, which are anchored in robust psychological theory and evidence-based
497 behaviour change techniques. The potential of remote support offered by digital and other
498 ‘smart’ technologies (in particular, to people with co-morbid conditions such as cognitive and
499 sight impairments) provides further scope to engage with vulnerable people, including those
500 living in rural communities.

501 ***Feasibility studies***

502 Finally, feasibility trials are an essential starting point for definitive randomised controlled
503 trials with respect to gauging patient acceptability and tolerability, and gleaning valuable
504 qualitative and quantitative data about recruitment, implementation, retention and indicative
505 effects. One novel method that could transform the interpretation of feasibility trials is the use

506 of Mendelian randomisation. In this context, feasibility studies can estimate the intervention
507 effects on intermediate endpoints that might be on the causal pathway to clinical outcomes.
508 Using a two-step process, the results of small-scale feasibility studies can be used to inform
509 much larger-scale two-sample Mendelian randomisation studies. This approach could
510 provide novel insight into the causal effects of an intervention on important intermediate
511 endpoints and possible long-term clinical endpoints (**see Figure 2**). In this way, Mendelian
512 randomisation can then be used alongside feasibility studies to optimise intervention
513 development and delivery, including more accurate outcome predictions for fully powered
514 conventional randomised controlled trials,⁷⁰ as outlined in Figure 2⁷¹.

515

516 **Conclusions**

517 It is timely to extend our knowledge of weight management by moving from epidemiology
518 studies to interventional research, as it relates to EBF in the context of cancer treatment and
519 survivorship. This increased knowledge will improve our understanding of the health
520 benefits to be gained from optimising body composition in people living with and beyond
521 common cancers, who constitute a significant health burden worldwide. Interventions need
522 to be complex but pragmatic in design, while encompassing multi-disciplinary
523 methodological approaches aimed at improving our understanding of causal mechanisms.
524 These endeavours are urgently needed to develop evidence-based strategies for mitigating
525 the adverse impact of EBF in a growing global population of cancer survivors⁶⁷ living in
526 increasingly obesogenic societies.

527

528 **Additional Information**

529 Table 1: Interpretation of studies evaluating anthropometric measures on mortality and
530 survival

531 Table 2: Range of core outcomes relevant in clinical trials of weight management

532 Figure 1: Possible explanations for the obesity paradox

533 Figure 2: Two-step Mendelian Randomisation procedure: Integration of feasibility

534 randomised controlled trial (RCT) results with MR to predict long-term effect of interventions

535

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539 **Authors' contributions**

540 A.S.A. Led the manuscript drafting, original concept, manuscript structure and drafting while

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546 **Consent for publication**

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548 **Data availability**

549 Not applicable

550 **Conflict of Interest**

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Legends

Table 1: Interpretation of studies evaluating anthropometric measures on mortality and survival

Table 2: Range of core outcomes relevant in clinical trials of weight management

Figure 1: Despite significant evidence that excess body fat (EBF) is associated with reduced cancer survival, data from a number of studies indicate that overweight and early obese cancer patients exhibit improved survival — this is known as the so-called ‘obesity paradox’. Although there are potential clinical and biological explanations for this in specific patient groups (red circles), many of these reports can be explained by methodological mechanisms (blue circles), including the inadequacy of BMI as a measure of adiposity

Figure 2: Introduction to Mendelian randomisation: Mendelian randomisation is a form of instrumental variable analysis that uses genetic variants as instruments to examine the causal effects of modifiable exposures on outcomes of interest. This method depends on the existence of genetic variants that are robustly associated with metabolite levels.

In the example outlined here, the results of a feasibility RCT of dietary interventions for the prevention of prostate cancer were carried forward to a large-scale Mendelian randomisation analysis to infer the causal effect of the interventions on prostate cancer risk via intermediate metabolites.

Cancer survivorship and excess body fatness – where are we in 2020?

Step 1 assessed the randomised effects of lycopene and green tea consumption for 6 months versus placebo on 159 serum metabolic traits, quantified by Nuclear Magnetic Resonance (NMR), amongst 133 men enrolled in the ProDiet randomised controlled trial. Step 2 used Mendelian randomisation to assess the effects of those metabolic traits altered by the intervention on prostate cancer risk, using genome-wide association studies (GWAS) summary statistics from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium. The lycopene intervention lowered circulating levels of pyruvate, a change that the Mendelian randomisation analysis suggested was associated with decreases in prostate cancer risk (a genetically instrumented SD increase in pyruvate increased the odds of prostate cancer by 1.29 (1.03, 1.62; $p = 0.027$)). Lycopene lowered levels of pyruvate, which our Mendelian randomisation analysis suggests may be causally related to reduced prostate cancer risk. By combining the results of a feasibility study with Mendelian randomisation, it has been possible to identify potential intermediate mechanisms through which interventions might be influencing cancer risk (see 767,68 (step 2)).