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Cancer prevention through weight control – where are we in 2020?

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Perspective– Cancer prevention through weight control – where are we in 2020?

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78

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

80 The Population Health Cancer Stream exists to promote research on key nutrition related factors

81 in the prevention of cancer. These are; diet and nutrition, alcohol, physical activity and obesity. In

82 calling for more research, the group is addressing an urgent need for more effective cancer

83 prevention strategies and interventions. We do not assign any judgement or stigma to any groups

84 or individuals on the basis of their lifestyle.

85

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94

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96 **Abstract**

97 Growing data from epidemiological studies highlight the association between excess body fat
98 and cancer incidence, but good indicative evidence demonstrates that intentional weight loss,
99 as well as increasing physical activity, offers much promise as a cost-effective approach for
100 reducing the cancer burden. However, clear gaps remain in our understanding of how
101 changes in body fat or levels of physical activity are mechanistically linked to cancer, and the
102 magnitude of their impact on cancer risk. It is important to investigate the causal link between
103 programmes that successfully achieve short-term modest weight loss followed by weight loss
104 maintenance and cancer incidence. The longer-term impact of weight loss and duration of
105 overweight and obesity on risk reduction also need to be fully considered in trial design. These
106 gaps in knowledge need to be urgently addressed to expedite the development and
107 implementation of future cancer control strategies. Comprehensive approaches to trial design,
108 Mendelian randomisation studies and data linkage opportunities offer real possibilities to
109 tackle current research gaps. In this paper, we set out the case for why non-pharmacological
110 weight management trials are urgently needed to support cancer risk reduction and help
111 control the growing global burden of cancer.

112

113 **Introduction**

114 Cancer causes one in six deaths globally and is now overtaking cardiovascular disease as the
115 leading cause of death across much of the world^{1,2}. Currently, tobacco use is the most
116 important single modifiable risk factor for cancer, but obesity (and its determinants — high
117 intakes of energy-dense, ultra-processed foods and drinks, and low levels of physical activity)
118 is becoming increasingly visible as the second most common cause of cancer. According to
119 the World Health Organisation (WHO), 1.9 billion adults and over 340 million children and
120 adolescents were living with overweight or obesity in 2016 (that is a Body Mass Index BMI
121 greater than 25kg/m²) and these numbers are projected to rise³. This situation is compounded
122 by global physical activity data suggesting that more than a quarter of the world's population
123 is insufficiently active⁴. Furthermore, overweight and obesity are occurring at earlier ages³,
124 thereby increasing lifetime exposure to associated risks. Current estimates suggest that
125 overweight and obesity could overtake smoking as the single biggest cause of cancer in UK
126 women in around 25 years⁵ and this premise is also echoed in international reports⁶. Of all
127 new global cancer cases in 2012, 481,000 (or 3.6%) were considered to be attributable to
128 excess Body Mass Index (BMI)⁷

129 The substantial reduction in lung cancer incidence in countries where public health initiatives
130 have brought about a significant decrease in smoking indicates the potential of primary cancer
131 prevention by societal interventions. The implementation of equitable, population-wide
132 programmes for obesity prevention and management are eagerly awaited, but sufficient
133 evidence already currently exists to justify a research focus on intentional weight loss and
134 cancer risk reduction trials. The ultimate objective of trials with positive results must be to
135 create further leverage for the development and implementation of policies aimed at improving
136 the health of the general public — not just the individuals who have the resources and
137 motivation to participate in individually-focussed weight loss programmes.

138 Pharmaceutical options are available to reduce the risk of obesity-related diabetes and heart
139 disease, but the portfolio of agents that reduce the risk of developing cancer is very limited.
140 Considerable amounts of data, including evidence from randomised controlled trials, support
141 the role of aspirin and tamoxifen in reducing colorectal cancer and breast cancer risk,
142 respectively, and, although further studies also support a role for other drugs, such as
143 metformin^{8,9} and statins¹⁰, in cancer prevention, the evidence is much weaker. The
144 effectiveness of these pharmaceuticals is relatively modest compared with drugs available for
145 treating cardiovascular risk factors (hypercholesterolemia, hypertension and insulin
146 resistance/hyperglycaemia). In addition, the mechanisms of action of these potential cancer
147 preventive agents are not well-established, and their pleiotropic and undesirable side-effects
148 must be considered¹¹ alongside evidence of inverse associations with mortality¹²

149

150 Based on the disappointing results of a number of cancer chemoprevention trials conducted
151 over the past three decades¹³, it is difficult to predict how long it will take to identify effective
152 drugs with low risk of side-effects, and we cannot afford to wait for pharmacological
153 approaches alone to prevent cancer risk. The benefit to potentially affected individuals and
154 their families and the direct and indirect economic implications of cancer risk reduction are far-
155 reaching. Addressing cancer prevention beyond pharmacological solutions has therefore
156 become a global imperative, and strategies that offer disease reduction should no longer be
157 ignored. We now have the evidence to demonstrate that intentional weight loss and weight
158 management as well as increasing physical activity offer much promise as cost-effective
159 approaches for reducing the risk of developing cancer

160

161 **Obesity and cancer**

162 The association between obesity and cancer has been reported and discussed in the literature
163 since the early part of the 20th century¹⁴ As population rates of overweight and obesity continue
164 to rise, so will the incidence of common cancers linked to excess body fat (EBF). As a

165 consequence, escalating costs attributable to future cancer treatments and the long-term
166 clinical management of associated comorbidities will place an unrelenting economic burden
167 on healthcare systems. Action needs to be taken now, otherwise our failure to seriously
168 address this topic will leave a sad legacy for the next generation

169

170 ***Evidence of an association between excess body fatness and cancer.***

171 There is a strong need to address the role of EBF in early life, as it has been demonstrated to
172 influence the risk of many diseases, including cancer, in adulthood. Hidayat *et al.*¹⁵ reported
173 associations between body fatness at a young age and the development in later life of eight
174 types of cancer. Jensen *et al.*¹⁶ subsequently reported from the Copenhagen School Health
175 Records Registry that children who were heavier or gaining more weight than average at 7 to
176 13 years of age (n= 257,623) had a significantly greater risk of adult colon cancer.

177 In adulthood, it seems that although the link between obesity and cancer is becoming more
178 apparent, the significance of weight gain across adult life remains largely ignored. Not only is
179 weight gain the pathway to overweight and obesity but it is also an independent risk factor for
180 post-menopausal breast cancer risk (around 6% per 5kg increase in adult weight¹⁷), which is
181 probably most relevant in women with a body mass index (BMI) <23.4 kg/m² at age 20 (who
182 are more likely to gain weight in adulthood than women with a BMI >23.4kg/m²).¹⁸

183 The latest (2018) World Cancer Research Fund (WCRF)/American Institute for Cancer
184 Research (AICR) expert report¹⁷ concluded that being overweight or obese throughout
185 adulthood increases the risk of cancers of the mouth, pharynx, larynx, oesophagus
186 (adenocarcinoma), stomach (cardia), pancreas, gall bladder, liver, colorectum, breast (post-
187 menopausal), ovary, endometrium, prostate (advanced) and kidney. In addition, a WHO
188 International Agency for Research on Cancer (IARC) Working Group found evidence relating
189 EBF to meningioma, thyroid cancer and multiple myeloma,¹⁹ and a hospital-based Danish

190 study of 313,221 patients reported overweight and obesity being related to haematological
191 and neurological cancers²⁰. The reported inverse associations between physical activity and
192 the risk of cancer at 13 sites, including some of the most common cancers (breast, lung, bowel
193 and kidney)^{21,22} reflects the important role of a physically active lifestyle in cancer prevention,
194 either via direct mechanisms, such as improved metabolic control or via its role in the
195 prevention of adult weight gain²³. Furthermore, studies show that structured exercise in
196 combination with support for dietary-led weight loss induces more weight loss than exercise
197 or diet alone and has the greatest impact on blood-borne biomarkers associated with common
198 cancers, including insulin resistance and circulating levels of sex hormones, leptin and
199 inflammatory markers^{24- 28}.

200

201 **Mendelian randomisation studies.**

202 In the absence of randomised clinical trials, evidence for causality can be strengthened by
203 Mendelian randomisation (MR) studies²⁹. MR is an instrumental variables method to appraise
204 causality within observational epidemiology, utilising germline genetic variants that are
205 robustly associated with potentially modifiable exposures as proxies ('instrumental variables')
206 for the risk factor of interest. As germline genetic variants tend to be randomly distributed with
207 respect to most human traits in the general population, MR studies are less likely to be affected
208 by the sorts of confounding factors that typically bias observational findings. Additionally, as
209 germline genotypes cannot be affected by the presence of disease, the generation of spurious
210 results through reverse causation is avoided. The objective is to identify modifiable
211 intervention targets (behavioural or therapeutic) on the intermediate causal pathway between
212 genetic factors and disease. DNA, although itself unmodifiable, operates through modifiable
213 pathways e.g. the proprotein convertase subtilisin/kexin type 1 (PCSK1) gene regulates
214 insulin synthesis; fat mass- and obesity-associated (FTO) gene promotes food intake. MR

215 exploits this to identify modifiable exposures that can be used for disease prevention and
216 therapeutic strategies.

217 Studies using MR support the influence of higher body fatness on greater risk of oesophageal,
218 gastric, pancreatic, renal, colorectal, endometrial and ovarian cancers³⁰⁻³³. Indeed, MR
219 analysis suggests that the obesity-related cancer burden has been substantially
220 underestimated³⁴. The volume and location of fat tissue are strong determinants of insulin
221 resistance and dyslipidaemia, and MR studies support strong effects of higher BMI on higher
222 fasting levels of insulin, glucose, triglycerides, remnant cholesterol, and lower high-density
223 lipoprotein (HDL) cholesterol³⁵. The adverse metabolic effects of higher fatness are already
224 evident in late childhood and might worsen with longer time exposure³⁶. Higher body fatness
225 also raises systolic and diastolic blood pressure, and impairs immunity via its association with
226 elevated pro-inflammatory factors such as interleukin-6³⁷. Several of these metabolic traits are
227 associated with an increased risk of obesity-related cancers, with MR evidence being
228 strongest for higher fasting insulin³⁸.

229

230 ***Excess body fatness and breast cancer risk.*** It is important to note that, from a life-course
231 perspective, higher body fatness in childhood and adolescence is inversely related to the risk
232 of pre-menopausal breast cancer as well as post-menopausal breast cancer³⁹, suggesting a
233 long-term protective effect of EBF on breast cancer risk later in life. Analysis from the cohort-
234 pooling project papers⁴⁰ on premenopausal breast cancer confirms that relative overweight at
235 age 18–24 is associated with a modest reduction in the risk of pre-menopausal breast cancer
236 up to the age of ~50 years, and additional analyses⁴¹ indicate that weight gain from ages 18–
237 24 to 35–44 or to 45–54 years is also inversely associated with breast cancer overall (e.g.
238 hazard ratio [HR] per 5 kg to ages 45–54: 0.96, 95% confidence interval [CI]: 0.95–0.98) and
239 with oestrogen-receptor(ER)-positive breast cancer (HR per 5 kg to ages 45–54: 0.96, 95%
240 CI: 0.94–0.98).

241 Evidence related to MR studies also indicates that a genetically predicted larger body size at
242 age 10 might protect against breast cancer in women independent of subsequent body size
243 at a mean age of 56.5 years⁴². These findings suggest that the effect of early-life body size
244 might persist into later life regardless of interventions to influence adult body size. There is
245 also evidence¹⁸ that early life body size exerts a protective effect even when accounting for
246 age at menarche. A better understanding of the mechanisms linking childhood body size and
247 timing of puberty with later breast cancer risk could help inform potential interventions.

248 Understanding the crossover effect of obesity with risk reduction before, and risk increase
249 after, menopause is poorly characterised and further work aimed at understanding the
250 biological mechanisms of how obesity, weight gain and weight change all impact on breast
251 cancer risk is needed¹⁷. However, the inverse association of obesity with pre-menopausal
252 breast cancer does not alter the overall harmful effects of obesity given that weight and weight
253 gain are positively associated with risks of postmenopausal breast cancer, several other types
254 of cancer, and other adverse health outcomes. In addition, women with obesity or who have
255 obesity diagnosed with breast cancer are more likely to have poorer outcomes than leaner
256 women (independent of their menopausal status)⁴³.

257

258 **Weight management — evidence of promise from observational studies**

259 Until 2010 the evidence that intentional weight loss in adulthood modifies cancer risk was
260 sparse, and mostly relied on self-reported body weight with relatively short follow-up periods.
261 However, long-term follow-up data from the Women’s Health Initiative cohort have since
262 reported that, after a mean follow-up of 11.4 years, women with modest weight loss (≥ 10
263 pounds from baseline weight during the initial three-year study) had a lower risk of endometrial
264 cancer compared with those who did not lose weight⁴⁴. This association was strongest among
265 women with obesity or that had obesity at baseline. In this cohort, a lower risk of breast cancer
266 among women who lost weight compared with women whose weight remained stable was

277 also reported⁴⁵. Similarly, the 17-year follow-up of the UK Women's Cohort Study has shown
278 a lower risk of post-menopausal breast cancer in those individuals who lost weight compared
279 to women with stable weight or those who gained weight⁴⁶.

270

271 The largest study to date on weight change and post-menopausal breast cancer is from the
272 Pooling Project of Prospective Studies of Diet and Cancer (DCPP),⁴⁷ which assessed data
273 from 180,885 women aged ≥ 50 years in whom 6930 invasive breast cancers were identified
274 at final follow-up. All women were surveyed at three points (baseline, first follow-up (mean of
275 5.2 years) and final follow-up (10 years)). Sustained weight loss was defined as no less than
276 2 kg lost between baseline and first follow-up, which was not regained by final follow-up. The
277 results demonstrated that, compared with women with stable weight, women with sustained
278 weight loss had a lower risk of breast cancer than women whose weight remained stable;
279 moreover, the larger the weight loss, the lower the risk. It is notable that even modest weight
280 loss (2–4.5 kg) was associated with a significant reduction in risk (HR 0.87, 95% CI 0.77–
281 0.99). Risk reduction was specific to women not using postmenopausal hormone replacement
282 therapy and the lowest risk was for women who sustained at least 9 kg of weight loss (who
283 were not taking hormone therapy).

284

285 **Weight management – indications from intervention studies**

286 Evidence for the impact of weight loss on cancer risk reduction is also emerging from
287 intervention studies, although no study has yet been designed (in terms of size and follow-up
288 period) specifically to assess the effects of weight loss on cancer incidence or mortality in the
289 general population. Several studies have evaluated the effect of bariatric surgery on cancer
290 risk, comparing people with obesity who underwent surgery with that of individuals in an
291 obesity (non-randomised) control group who did not. According to a systematic review,

292 bariatric surgery was reported to be associated with a reduction in the incidence of overall
293 cancer (Pooled Odds Ratio (POR) = 0.72: 95% CI 0.59–0.87) and in the incidence of obesity-
294 related cancers (POR=0.55: 95% CI 0.31–0.96)⁴⁸. The cancer-protective effect of bariatric
295 surgery seems to be more pronounced in women than in men, and most marked for a
296 reduction in breast cancer risk. It is notable that the favourable impact of bariatric surgery on
297 cancer risk for adults in mid- and later-life occurs within a relatively short follow-up period and
298 is independent of physical activity. However, people undergoing bariatric surgery do not
299 necessarily reflect the general overweight and obese population, and the physiological
300 response following acute weight loss might in itself produce effects that might not be matched
301 by weight loss induced through lifestyle interventions⁴⁹. A systematic review of weight loss
302 trials⁵⁰ reported a significant reduction in the risk of all-cause mortality, cardiovascular mortality
303 and cancer mortality. Furthermore, in 2020 the Look Ahead Research Group reported⁵¹ that
304 an intensive lifestyle intervention trial of 5145 participants which targeted weight loss
305 successfully lowered incidence of obesity-related cancers by 16% in adults with
306 overweight or obesity and type 2 diabetes after a median follow of 11 years,
307 highlighting the potential success of such interventions in cancer risk reduction

308

309 **Considerations in the design of trials investigating the influence of weight loss on**
310 **cancer risk**

311 Irrespective of the mode of weight loss, it is important to investigate whether or not
312 programmes that successfully achieve short-term modest weight loss followed by weight loss
313 maintenance confer benefit on cancer incidence. The potential effect of latency of risk
314 reduction following weight loss, as well as the duration of overweight and obesity, need to be
315 fully considered in trial design. Furthermore, it is important to identify whether or not the
316 benefits of weight loss are offset by any subsequent regain in weight. There is much to be
317 learnt from highly successful diabetes prevention programmes based on change in caloric

318 intake and increased physical activity for weight loss^{52,53} and it is particularly notable that in a
319 15-year follow-up of the Diabetes Prevention Program, the incidence of diabetes still remained
320 lower — by 27% — in the lifestyle intervention group compared with the placebo group⁵⁴.

321

322 ***The influence of physical activity***

323 Whilst reduced caloric intake plays a greater role than physical activity in weight loss⁵⁵, the
324 latter might be particularly important in weight loss maintenance⁵⁶. However, it is likely that
325 physical activity confers additional benefits on the reduction of cancer risk, for example
326 through modulation of immune-regulatory pathways⁵⁷, reduced oxidative stress⁵⁸, epigenetic
327 changes⁵⁹ and reduced telomere attrition⁶⁰, that may be independent of its effects on body
328 weight²¹. A 2020 MR study using data from the UK Biobank showed that physical activity is
329 inversely associated with breast and colon cancer risk, independent of its effect on adiposity
330 and the association between physical activity and cancer incidence at 10 sites was shown to
331 be independent of BMI⁶¹. Furthermore, strength training, which builds skeletal muscle mass,
332 is inversely associated with the risk of bladder, kidney and colorectal cancer^{62,63}.
333 Improvements in insulin sensitivity and glucose homeostasis induced by aerobic exercise
334 and/or strength training⁶⁴ could reduce the risk of cancers associated with insulin resistance
335 (and associated cellular signalling pathways), including cancers of the colon, liver, pancreas
336 and endometrium⁶⁵.

337

338 ***The influence of dietary factors***

339 Similarly, it is important to consider the independent impact of dietary factors both in terms of
340 macronutrient and micronutrient composition. Strong evidence exists for a protective role of
341 several dietary factors in colorectal cancer (wholegrains, foods containing dietary fibre and
342 dairy products) but less so for other cancer sites⁶⁶. Whilst there has been some promising

343 evidence for the beneficial role of fruit and vegetables in reducing cancer risk the overall
344 impact on cancer burden is largely limited to cancers of the respiratory and upper digestive
345 tract^{66,67}. Furthermore, enthusiasm for micronutrient supplementation to reduce cancer risk
346 has diminished following a number of randomised control trials that have produced evidence
347 of an associated increased risk of cancer^{68,69}. The lack of impact of single nutrients/foods on
348 cancer prevention does not mean that the quality of the diet can be ignored. Cancers arising
349 from aberrant metabolic pathways are likely to be influenced by the same nutrients and foods
350 that are associated with the risk of diabetes⁷⁰ and there is some evidence that healthy dietary
351 patterns (diets that are high in vegetables, fruit, whole grains, legumes and nuts) are
352 beneficial. In turn, foods that promote weight gain (e.g. sugar-sweetened beverages), along
353 with red and processed meats and alcohol, should be minimised — alcohol consumption is
354 not only a contributor to caloric intake but also a recognised carcinogen¹⁷

355 ***Weight management***

356 Focus on weight management enables a lifestyle pattern combining diet quality and quantity,
357 alcohol intake and physical activity to be promoted and tested. Given the tendency for lifestyle
358 behaviours to cluster/co-occur⁷¹, implementation of equitable interventions that impact on
359 several key areas of lifestyle offer considerable scope for reducing the overall disease burden.
360 Although many unanswered questions exist within lifestyle interventions, with respect to dose,
361 duration, type (for physical activity), caloric composition and diet quality (in terms of food
362 intake), and how best to support long-term adherence, there is much that we can learn from
363 longer-term lifestyle trials including those focusing on diabetes prevention. For example,
364 intervention design no longer focuses on knowledge exchange alone but integrates goal -
365 based behavioural interventions, the use of lifestyle coaches, frequent contact and support
366 and “toolbox strategies” to enable individual tailoring⁷². Furthermore, recent work has
367 highlighted the impact of using behavioural change techniques to support changes in diet and
368 physical activity⁷³.

369

370 **Weight loss trials — challenges and opportunities**

371 The potential for ‘megatrials’ to answer nutritional questions has been described by
372 Trepanowski and Ioannidis⁷⁴ to address challenges such as selective reporting, small sample
373 size, short length of follow-up and high costs (trials of non-pharmacological interventions are
374 generally publicly funded, with relatively low budgets, which makes large sample sizes and
375 lengthy follow-up protocols prohibitive). These challenges are common in nutritional trials (as
376 with other clinical areas) and it is clear that the methodological rigour of complex dietary
377 behavioural trials needs to improve. In reality, large randomised controlled trials are likely to
378 improve our understanding of the impact of weight management on cancer risk but will need
379 to be considered alongside other data sources such as pooled cohort studies⁷⁵, triangulated
380 MR approaches (see Figure 1)⁷⁶ and network meta-analysis⁷⁷. The science of trial design⁷⁸
381 now offers a much clearer pathway for designing and addressing trial challenges, enabling
382 researchers to optimise recruitment from populations of interest, incorporate intervention
383 features (content, implementation, fidelity and adherence), comparator groups, adaptive trial
384 design⁷⁹ and to collect long-term outcomes. The key here is to assess the body of evidence
385 appropriately by recognising the inherent weaknesses in the various research designs that
386 contribute to it.

387

388 Although three decades of trials of behavioural weight loss programmes such as the Diabetes
389 Prevention Program have successfully demonstrated a significant reduction in the incidence
390 of diabetes, weight loss programmes for cancer prevention have not received much funding.
391 A 21st century rationale (as described by Ballard et al⁸⁰) for this lack of investment points to a
392 lack of good interim biomarkers, the need for prohibitively large sample sizes, uncertainties
393 about life stage and appropriate ‘dose’ of intervention, the need to achieve sustained
394 behaviour change and the apparent desire for genetic discoveries. There are also concerns

395 that people who attempt and fail to adhere to weight loss regimens might experience negative
396 emotional responses and, indeed, self-blame if a subsequent diagnosis of cancer is made.
397 However, the past decade has seen a portfolio of weight loss regimens combining novel
398 dietary approaches, motivational technologies and implementation science approaches, which
399 will help to optimise adherence and provide supportive behaviour change strategies for weight
400 loss trials^{81,82}. Although multi-component interventions offer significant challenges, such
401 approaches have been successfully tested in diabetes⁸³ and cognitive function⁸⁴ contexts, and
402 are feasible to implement. Modern wearable technologies to motivate and support behaviour
403 change, remote objective data collection and record linkage to routine clinical or registry data
404 for follow-up (of at least a decade) make some of the difficulties in cancer prevention trials
405 more manageable. Furthermore, improvements in trial design, understanding of intervention
406 content and dose, and knowledge regarding the provision of effective long-term support for
407 behaviour change make successful cancer prevention trials increasingly plausible.
408 Nevertheless, an important challenge for primary prevention trial design is the identification of
409 clinically meaningful short- and longer-term health outcomes. The search for robust and
410 clinically relevant surrogate markers (e.g. adenoma recurrence in colorectal cancer,
411 mammographic density, hormone levels in breast cancer etc.) continues, and such markers
412 would add considerable confidence to expensive intervention studies with long-term follow-
413 up. However, it is also important to note that studies of chemoprevention (e.g. aspirin) that
414 have cancer development as their primary outcome have been funded, and lifestyle
415 interventions could do likewise.

416

417 ***Weight management and high-risk populations.***

418 One notable population of interest for weight management trials includes people who are
419 known to be at a higher risk of developing cancer, including those with a family history of
420 colorectal or breast cancer who are already undergoing surveillance procedures. In a large
421 international multicentre trial of aspirin in patients with Lynch syndrome (hereditary non-

422 polyposis colorectal cancer), Movahedi *et al.*⁸⁵ reported that participants with obesity were
423 2.41 times (95% CI, 1.22 to 4.85) more likely to develop colorectal cancer than participants
424 with under- and normal-weight, and their risk increased by 7% for each 1 kg/m² increase in
425 BMI. There is considerable interest in weight management in women with a family history of
426 breast cancer, although the greatest efforts to date have focussed on physical activity
427 interventions. Gramling *et al.*⁸⁶ reported from the Women’s Health Initiative observational study
428 that healthy lifestyles (i.e regular exercise, healthy body weight on the basis of BMI and <7
429 alcoholic drinks per week) led to a reduction in the risk of breast cancer in postmenopausal
430 women, and the degree of this benefit was similar for women with and without a family history
431 of breast cancer. A review by Pettapiece-Phillips *et al.*⁸⁷ reported evidence of a protective role
432 of a healthy body size and regular physical activity among *BRCA* mutation carriers, notably in
433 adolescence and early adulthood. A number of feasibility or pilot trials of weight management
434 have been undertaken in this high-risk population, including an assessment of the Diabetes
435 Prevention Program (with modifications) on breast cancer risk biomarkers⁸⁸. Intervention
436 studies involving diet and physical activity⁸⁹, intermittent energy restriction⁹⁰, endurance
437 training and nutrition counselling on the Mediterranean diet ⁸¹ in individuals at increased risk
438 of breast cancer are currently underway. These developmental studies point to the feasibility
439 of initially ‘testing’ complex intervention trials in high-risk populations and should provide both
440 rational and relevant platforms for planning definitive average-risk population level randomised
441 controlled trials.

442

443 **Conclusions**

444 The need for much greater investment in research into cancer prevention is beyond question,
445 and yet the current spend is only around 3% of the UK cancer research budget⁹¹. Worldwide,
446 excess weight is associated with the development of at least 480,000 new cancer cases each
447 year⁷. The bulk of current observational evidence on weight loss and obesity-related cancers

448 suggests that decreasing body weight, reducing EBF and maintaining losses, by even
449 relatively modest amounts, can impact on future cancer risk. It is important to note that most
450 obese people who lose weight will remain in the obese category but will have reduced cancer
451 risk by even modest weight loss *per se*, which should therefore increase motivation
452 for participating in interventions. However, clear gaps remain in our understanding of how
453 changes in body fat or increased levels of physical activity are mechanistically linked to a
454 decreased incidence of cancer. In addition, understanding the impact of different measures of
455 EBF (e.g. body mass index, central obesity as assessed by waist circumference, bioelectrical
456 impedance, DXA, etc.) adds to the complexity of identifying possible solutions^{11,12,92}. These
457 gaps need to be urgently addressed to expedite the development and implementation of future
458 cancer control strategies.

459 Well-designed trials, providing robust evidence of impact, are crucial for efforts to garner
460 funding for weight management programmes aimed at reducing cancer risk. To date, trials of
461 weight management and cancer prevention have almost exclusively been confined to
462 feasibility work. The time has come for an international commitment to decreasing cancer
463 burden and this commitment includes the development of large-scale intervention trials of
464 weight management for primary prevention of obesity-related cancer — a point also raised in
465 the paper on critical research gaps and recommendations in colorectal cancer⁹³. This need is
466 urgent and the time to act is now!

467

468 **Additional Information**

469 Expected effects of lowering BMI on cancer risk –how Mendelian Randomisation can guide
470 research [Figure 1]

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474 **Authors' contributions**

475 A.S.A led the manuscript drafting, original concept, manuscript structure and drafting.
476 A.G.R; J.M.S.; J.B.; J.C.; A.J.C.; A.K.; E.R.; F.S.; S.T.; R.M.M.; were involved in the original
477 concept, manuscript structure and drafting. All authors approved the final version of the
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479 **Ethics approval and consent to participate**

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483 **Data availability**

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485 **Conflict of Interest**

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810 Legends

811 Figure 1: Current estimates from genetically informed Mendelian randomisation (MR) studies
812 can be used to set expectations for results of future randomised controlled trials. A recent
813 meta-analysed MR estimate of BMI for colorectal cancer (from Jarvis et al. 2016. *Br J*
814 *Cancer*) suggests that a 5 kg/m² lower BMI would reduce risk of developing colorectal

815 cancer by approximately 20%. This MR estimate reflects lifetime exposure to this relatively
816 lower BMI, and so the magnitude of reduced colorectal cancer risk in response to short-term
817 BMI reduction is expected to differ.

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