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Title: **Living with cancer and multi-morbidity: the role of primary care**

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23   *Purpose of review*:

24   As more people live longer with cancer, the number of patients with cancer and multiple

25   other chronic conditions (multi-morbidity) has increased. The presence of multi-morbidity

26   impacts on all stages of cancer care, from prevention and early detection through to end of

27   life care, but research into cancer and multi-morbidity is in its infancy. This review explores

28   the impact of multi-morbidity on adults living with (and beyond) cancer, with particular

29   attention paid to the role of primary care in supporting patients in this situation.

30

31   *Recent findings*:

32   Patterns of multi-morbidity vary depending on cancer type and stage, as well as population

33   characteristics and available data (e.g. number of conditions assessed). Cancer survivors

34   are at increased risk of developing other chronic conditions, due to a combination of shared

35   risk factors (e.g. smoking and obesity), effects of cancer treatments, and psychosocial

36   effects.

37

38   *Summary*:

39   Primary care has a central role to play in supporting multi-morbid adults living with cancer,

40   providing holistic care of physical and mental well-being, while taking treatment burden and

41   social circumstances into account. New models of person-centred and personalised cancer

42   care include holistic needs assessments, care planning, treatment summaries, and cancer

43   care reviews, and depend on improved communication between oncologists and primary

44   care colleagues.

45

46   *Keywords:* cancer, multi-morbidity, co-morbidity, primary care, treatment burden

Introduction

Multi-morbidity is usually defined as the co-occurrence of two or more long-term conditions in any individual. The term promotes a person-centred approach, in contrast to the more disease-centred term "co-morbidity" where a patient is identified by their index condition and any additional health problems are considered co-morbidities. It is now widely recognised that most people with any long-term condition are more likely to have multi-morbidity than to have a single condition – multi-morbidity is the norm in chronic illness (1). Furthermore, the onset of multi-morbidity occurs roughly 10 to 15 years earlier in patients living in the most deprived areas compared to the most affluent (1). These observations have significant implications for health care, research and medical education, as outlined in the landmark 2012 Lancet paper on the epidemiology of multi-morbidity (1). Multi-morbidity matters because it is associated with adverse health outcomes, including higher mortality, poor quality of life, lower functional status, and higher rates of hospital admissions (2-4). Yet the optimal healthcare response to patients with multi-morbidity is unclear, and the majority of existing evidence is in populations of older people with little research on the larger number of people under 65 years of age with multi-morbidity (1, 5, 6).

In relation to cancer, the presence of multi-morbidity impacts on all stages of care, from prevention and early detection through to end of life care (7-10). Cancer prevention is complicated by multi-morbidity because many of the modifiable risk factors associated with the prevention of cancer (e.g. smoking, alcohol, poor diet, physical inactivity) are also linked to long-term conditions such as diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), arthritis, and mental health conditions, the symptoms of which can make enacting behaviour change more challenging. Furthermore, many people have multiple unhealthy behaviours, with particular clustering in areas of socio-economic deprivation (11), adding further complexity (12).

74 Detecting cancer early can also be affected by multi-morbidity, with some patients having

75 their cancer diagnosed earlier due to frequent contacts with health services, and others

76 being diagnosed later if they attribute symptoms to comorbid conditions, as in the case of

77 COPD and lung cancer (13).

78

79 The focus of this review, however, will be on the impact of multi-morbidity on adults living

80 with (and beyond) cancer, with particular attention paid to the role of primary care in

81 supporting patients in this situation. There is a complementary review in this issue which

82 focusses on multi-morbidity in older adults with cancer (REF Corbett and Bridges paper)

83

84 We searched PubMed, EMBASE and Google Scholar using search terms in three broad

85 categories relating to multi-morbidity, cancer, and primary care. We also used citation

86 searching and articles from our personal collections to allow a thorough review of the

87 subject. The majority of research articles we reviewed were published within the last 18

88 months and all were written in English.

89

90 **Common patterns of multi-morbidity in adults living with cancer**

91 Cancer incidence increases with age, as does the incidence of multi-morbidity. With ageing

92 populations in most high-income countries, people are now more likely to develop cancer

93 while already having other chronic conditions. Furthermore, with recent advances in cancer

94 diagnosis and treatment, people are also living longer with cancer, and therefore more likely

95 to develop other chronic diseases during their lifetime.

96

97 Figure 1 provides an illustration of the extent of multi-morbidity for people with any cancer, in

98 a nationally representative sample of the Scottish population (1). Particularly common co-

99 morbidities were painful conditions, depression, anxiety, coronary heart disease, diabetes,

100 and COPD, and all of these were more prevalent in the most deprived decile compared to

101 the most affluent.

102

106

More recently, Zemedikun et al analysed UK Biobank Data to establish patterns of multi-morbidity in adults aged 40 to 69 years (14). 19% of study participants had 2 or more chronic conditions, with hypertension, asthma and cancer being the three most common conditions (cancer prevalence was 8.3%). Cancer was associated with nine other conditions in their cluster analysis, including hypertension, asthma, anxiety, depression, eczema, irritable bowel syndrome, and migraine.

113

Patterns of multi-morbidity vary depending on cancer type and stage, as well as population characteristics and limitations of data (e.g. number of conditions assessed). For example, Williams et al assessed co-morbidities in older adults with different cancers in the US (15)*. Overall, 92% of participants reported one or more co-morbid condition, with a mean of 2.7 conditions (range 0 to 10). Approximately half of all patients reported arthritis and hypertension, but there were important differences in co-morbidities by cancer type. Circulatory problems, diabetes, heart disease, and depression were also common (affecting around 20%), in keeping with other studies that have explored co-morbidities associated with different cancers (16, 17).

123

The mechanisms underlying relationships between certain cancers and certain co-morbidities have been explored. Many cancers share common risk factors (smoking, obesity, alcohol) with conditions such as hypertension, cardiovascular disease (CVD), diabetes, and COPD, but there is recent evidence to suggest that certain chronic diseases themselves (e.g. diabetes and chronic kidney disease) may predispose to cancer (18).

129

130   Some pre-existing conditions also increase the risk of developing cancer treatment-related

131   complications. For instance, patients with cardiovascular disease, diabetes or

132   hypercholesterolaemia are more likely to develop cardiovascular side effects, especially left

133   ventricular dysfunction, from anticancer therapy (19)*. Similarly, patients receiving androgen

134   deprivation therapy in the treatment of prostate cancer have been shown to be at increased

135   risk for developing diabetes (20).

136

137   **Illness and treatment burden in multi-morbid adults living with cancer**

138   There are several important implications of multi-morbidity for adults living with cancer. As

139   noted above, multi-morbidity is associated with lower quality of life and poorer functional

140   status and this can affect cancer treatment outcomes and therefore treatments offered. The

141   concepts of illness and treatment burden may be helpful in guiding discussions and decision-

142   making related to cancer treatment and support.

143

144   Illness burden refers to the "work" involved in living with a chronic illness and includes

145   physical, emotional, social and existential elements (10). This burden of illness is closely

146   related to the number and severity of symptoms (e.g. pain, fatigue, breathlessness) that a

147   patient is experiencing, but is also influenced by the patient's capacity to understand and

148   manage their different conditions and symptoms.

149

150   Treatment burden refers to the "work" that patients (and their families or carers) are asked to

151   perform to respond to the requirements of their healthcare providers, as well as the impact

152   that this work has on patient functioning and wellbeing (21). Research on treatment burden

153   in patients with multi-morbidity has highlighted issues such as polypharmacy and complex

154   medication regimes, fragmentation of care across different specialities, and challenges

155   related to lifestyle changes and self-monitoring (22, 23).

156

157   Figure 2 shows an adaptation of the cumulative complexity model, a patient-centred

158   framework that incorporates illness and treatment burdens but also emphasises the

159   workload-capacity balance (24). Capacity in this context refers to the abilities, resources, or

160   readiness to address the demands of illness and treatment. These resources include

161   physical and mental functioning, socioeconomic resources, social support, literacy, and

162   attitudes/beliefs (24).

163

164   [INSERT FIGURE 2. Legend = The cumulative complexity model (adapted from Shippee et
165   al (24)

166

167   A recent qualitative systematic review and synthesis of evidence on the experience of

168   cancer and co-morbid illness suggests there is still considerable room for improvement in

169   addressing the workload-capacity balance to better support multi-morbid adults living with

170   cancer (25)**. The authors identified five key themes from the 31 included studies: 1) the

171   interaction and impact of cancer and co-morbidity (which affected not only quality of life and

172   recovery, but also treatment decisions); 2) the complex symptom burden and experience

173   (which was variable and mediated for some by cancer stage and severity but also led to

174   blurring of symptoms and attribution difficulties for others); 3) illness expectations and

175   identity when facing complex illness (which was influenced by past experience of illness as

176   well as notions of ageing and expectations of ailing health and function); 4) managing

177   medications and self-management (which emphasised the need for shared care and

178   resources to support self-management); and 5) the role of primary and secondary care in

179   meeting survivorship needs (which highlighted the at times fragmented experience of care).

180

181   Some of these findings reflect wider trends in cancer treatment, such as the shift towards

182   shorter inpatient stays and a greater emphasis on management (and self-management)

183   closer to home, with patients and carers encouraged to be more responsible for their care.

184   Furthermore, the increasing use of oral chemotherapy has presented new challenges for

185 patients and healthcare providers (26). Oral regimens can be complex, comprised of

186 multiple medications with varying dosages and instructions, and requiring patients and

187 primary care practitioners to recognise side effects and potential interactions.

188

189 Common side effects of oral chemotherapy treatments include nausea, fatigue, diarrhoea,

190 oral mucositis, sleep disturbance, skin conditions (e.g. rashes, blisters, dry skin), and

191 neuropathy. Managing these at home may require dose modifications, interruptions,

192 discontinuing treatment, or admission to hospital, all of which require communication

193 between patients and their healthcare providers, ideally in primary and secondary care.

194

195 Patients with multi-morbidity are more likely to be prescribed multiple medications (known as

196 polypharmacy) and primary care practitioners are well placed to assess polypharmacy and

197 identify potentially inappropriate medications (PIMs), with a high risk-to-benefit ratio. A

198 recent study of older patients with breast and colorectal cancer found that roughly 30% were

199 on PIMs (27). A similar study found even higher rates of PIMs (over 65% for patients with

200 colorectal cancer) and significant associations with increased healthcare utilisation and

201 higher costs (28).

202

203 **The role of primary care in supporting multi-morbid adults living with cancer**

204 The role of primary care in supporting patients living with and beyond cancer was well

205 summarised in a 2018 review in this journal, which emphasised the strengths of primary care

206 as contact, comprehensiveness, continuity and coordination (29). These four pillars of

207 primary care are particularly important in the context of adults with multi-morbidity, who

208 account for over half of all GP consultations and nearly 80% of prescriptions (30).

209

210 Despite these apparent strengths, it is well recognised that GP input during cancer treatment

211 and survivorship phases is highly variable, both within and between countries (31). Rubin et

212 al outlined the following areas as being particularly important for primary care practitioners

213   (PCPs) to optimise care: long-term and late effects of cancer treatment; psychosocial

214   effects; detection of recurrence; prevention; and models to deliver survivorship care (31). All

215   of these aspects of care are potentially more complex in the presence of multi-morbidity.

216

217   Knowledge of the long-term and late effects of cancer treatment was recognised as one of

218   several learning gap for PCPs in relation to cancer survivorship care (32). While primary

219   care practitioners (GPs and practice nurses) may be well used to supporting adults with

220   multi-morbidity, providing holistic care of physical and mental well-being, and taking social

221   circumstances into account, it is clear that people living with cancer have unmet physical,

222   psychosocial and spiritual needs (33, 34).

223

224   Psychosocial needs of multi-morbid patients with cancer were explored in a qualitative study

225   from Australia which showed how multi-morbid illness representations can influence self-

226   management (35)*. Most of the study participants – who had cancer and anxiety/depression

227   – viewed the conditions as intertwined. A range of cancer-related consequences were

228   perceived as causing anxiety/depression, including visible scars from treatment, physical

229   disabilities, hair loss, inability to work, fertility difficulties, and loss of independence (35)*.

230

231   The fear of cancer recurrence (FCR) was common and manageable for most, but for some

232   people it could become debilitating, resulting in unhelpful coping behaviours (e.g. becoming

233   "engrossed in Dr Google") and worsening their anxiety/depression. This is in keeping with

234   the growing body of research on FCR (36, 37), suggesting that screening for and monitoring

235   of psychosocial effects (such as FCR) should be a routine part of cancer care reviews in

236   primary care.

237

238   The role of primary care in the preventive care of cancer survivors is also gaining increasing

239   attention (38). Preventive care relates to the prevention of morbidity and premature mortality

240   in individuals and is traditionally considered in terms of primary, secondary and tertiary

241 prevention. For cancer survivors, the prevention of further cancers and cardiovascular

242 disease are priorities. One recent study found that approximately 25% of older adults (≥65

243 years) and 11% of younger adults had a history of prior cancer, with most of these new

244 cancers diagnosed in different anatomic locations (39)*. Cancer survivors are at increased

245 risk of CVD, due to a combination of shared risk factors (e.g. smoking and obesity),

246 cardiotoxic effects of cancer treatments, and sub-optimal CVD prevention (40). Primary care

247 therefore has a key role in supporting health behaviour change related to smoking, alcohol,

248 diet and physical activity, as well as in optimising adherence to statins when indicated.

249

250 With regard to models of care for supporting multi-morbid adults living with cancer, there is

251 no consensus on the optimal approach, although all models include improved

252 communication between oncologists and primary care colleagues (41). Traditional follow-up

253 care based on routine appointments for years following treatment is now considered to be

254 neither sustainable nor effective (42). In the UK, recommendations for person-centred and

255 personalised (stratified) care for people affected by cancer include holistic needs

256 assessments, care planning, treatment summaries (including information about risk of

257 recurrence and known risks from treatments), access to educational 'health and wellbeing'

258 events, and cancer care reviews (43).

259

260 **Implications for future research**

261 Supporting people with multiple chronic illnesses (multi-morbidity) to live well with (and

262 beyond) cancer requires robust evidence of what works, for whom, and in what

263 circumstances. At present, the majority of clinical practice cancer guidelines are derived

264 from clinical trials that exclude medically complex older adults (and those from poorer socio-

265 economic backgrounds (44)). This is often for rational scientific reasons – for instance, to

266 avoid interactions of other prescribed medications with the trial drug – but there are growing

267 calls for cancer trials to be more pragmatic and less exclusive (45, 46).

268

269   Research in patients with cancer and multi-morbidity poses several methodological

270   challenges due to heterogeneous study populations, difficulties with recruitment and a

271   variety of relevant outcome measures (47). Patient-reported outcome measures will

272   increasingly inform the development of health services and other forms of support to limit the

273   disruption to everyday lives of patients (and their carers) who are living with cancer (42, 48).

274

275   **Conclusion**

276   As more people live longer with cancer, the number of patients with cancer and multiple

277   other chronic conditions will also increase. Primary care has a central role to play in

278   supporting multi-morbid adults living with cancer, identifying physical, psychosocial and

279   spiritual needs, and signposting to financial support if necessary.

280

281   It has been ten years since May and colleagues called for healthcare to be "minimally

282   disruptive" to patients with chronic illness, tailoring treatment regimens to the realities of

283   patients' daily lives (23). Healthcare practitioners must take into account both workload

284   demands and patient capacity when supporting patients living with cancer, asking questions

285   such as: "Can you really do what we are asking you to do?" and "Do you think what we are

286   asking you to do is the right thing for you?"(49)

287

288

289 **Key points**

290 - As people live longer with cancer, multi-morbidity is becoming the norm, with

291   implications for health care, research and medical education.

292 - There is a strong social gradient in multi-morbidity, with onset 10-15 years earlier in

293   more deprived areas.

294 - Health services need to consider illness and treatment burden, as well as patient's

295   existing capacity and resources, when discussing cancer treatments.

296 - New models of person-centred and personalised cancer care depend on improved

297   communication between oncologists and primary care colleagues.

298

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304 **Conflicts of interest**

305 None

References and recommended reading

Papers of particular interest, published within the 18 month period of review, have been highlighted as:

* of special interest

** of outstanding interest

15* This data linkage study highlights the impact of co-morbid conditions on adults with cancer: they are common, impair function, and are associated with increased risk of all-cause mortality.

19* UK editorial which introduces the emerging speciality of cardio-oncology and summarises its three distinct areas; the acute management of cardiovascular complications; the long-term screening of patients post-chemotherapy; and the planning of chemotherapeutic regimens in patients with established, or at high risk of, cardiovascular disease.

25** A qualitative systematic review and synthesis of evidence on the experience of cancer and co-morbid illness. The five themes identified in the review encapsulate the main challenges that multi-morbidity presents to high quality cancer care. They were: 1) the interaction and impact of cancer and co-morbidity; 2) the complex symptom burden and experience; 3) illness expectations and identity when facing complex illness; 4) managing medications and self-management; and 5) the role of primary and secondary care in meeting survivorship needs.

35* This qualitative study explored illness representations in patients with cancer and anxiety/depression. It highlights the common psycho-social impacts of cancer, such as effects on sense of identity and sexuality, and fear of cancer recurrence, as well as showing how patients' understandings of cancer and other conditions interact.

39*	This study linked data from the US population-based Surveillance, Epidemiology, and End Results (SEER) program of cancer registries (1975-2013) for 740 990 persons newly diagnosed with cancer from January 2009 through December 2013. It shows that a substantial proportion of patients diagnosed with incident cancer in the United States have survived a prior cancer, and highlights that these patients are often excluded from clinical trials and underrepresented in observational research.

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