

LONELINESS AND ITS RELATIONSHIP WITH CANCER

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ABSTRACT

Cancer is one of the leading and most feared non-communicable diseases diagnosed in humans. Despite significant improvement in cancer screening, diagnostics, and therapeutics, it is far from being controlled and its incidence is expected to continue to rise worldwide. Cancer is expected to become the leading cause of global deaths in the coming decades. As a result, cancer preventive therapy is experiencing a noticeable upsurge in interest. Loneliness, a pernicious emotional and social phenomenon, is not only a risk factor for cancer and but is also closely associated with lifestyles. Healthy lifestyles play an important role in cancer prevention, and positively modulate every aspect of cancer throughout its course. Unfortunately, loneliness is ubiquitous in our society, and its prevalence appears to be rising. Further, cancer itself promotes the development of loneliness. The relationship between loneliness and cancer is intricate and bidirectional and is associated with ominous outcomes. This manuscript briefly reviews this deleterious relationship.

Keywords: Loneliness, Social Isolation, Cancer, Depression, Unhealthy Lifestyles.

INTRODUCTION

Cancer is a major public health problem worldwide (<https://www.who.int/news-room/fact-sheets/detail/cancer>). The International Agency for research on cancer and the World Health Association (WHO), indicates that in 2018, there were 18.1 million new cases globally (<https://gco.iarc.fr/>). The most common cancers were those affecting the lung, breast, and prostate (<https://gco.iarc.fr/>). Cancer-related deaths reached 9.6 million in 2018 (<https://www.iarc.fr/featured-news/latest-global-cancer-data-cancer-burden-rises-to-18-1million-new-cases-and-9-6-million-cancer-deaths-in-2018/>), and cancer is now the second leading cause of death in the world (Bray et al., 2019). In the high-income countries, cancer has already overtaken cardiovascular diseases as the leading cause of death (Mahase, 2019). It may become the leading cause of global deaths in the coming decades (Dagenais et al., 2020). Cancer is also pervasive in the United States (US) (Siegel et al., 2018). An American male has a 40% lifetime risk while an American female has a 38% lifetime risk of developing cancer (Noone et al., 2018). Cancer survival, although improving, remains dismal and about 40% of cancer sufferers will not survive 5 years (de Moor et al., 2013). Second primary cancers are also on the rise and now account for 15 to 20% of all cancer diagnoses (Demoor-Goldschmidt & de Vathaire, 2019). It was estimated that the US spent \$173 billion on cancer care in 2020 (Mariotto et al., 2011). According to WHO, Europe has one-quarter of the global cases of worldwide cancers, although comprising only one-eighth of the total world population (<https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics>). Cancer is also common in China

(Yu et al., 2015), the world's most populous country, and has become its leading cause of death (Feng et al., 2019).

Loneliness is a common disorder in our society (<https://www.cigna.com/about-us/newsroom/studies-and-reports/combatting-loneliness/>) and is a major risk factor for several non-communicable diseases, including cancer (Williams et al., 2009). Lonely people also tend to lead unhealthy lifestyles and are more depressed and these contribute to the increased risk (Richard et al., 2017; Cacioppo et al., 2018). It is estimated that unhealthy lifestyles are responsible for almost 40% of all cancers (Song & Giovannucci, 2016). Studies from China indicate that the major unhealthy lifestyles responsible for cancer deaths in 2013 were smoking (Islami et al., 2017). Hepatitis B virus (HBV) infection, and low fruit/vegetable intake in men and HBV infection, low fruit/vegetable intake, and second-hand smoke exposure in women (Islami et al., 2017). Loneliness in cancer also leads to increased fatigue, more pain, frequent sleep disturbance (Jaremka et al., 2014), a poor quality of life, and higher mortality (Drageset et al., 2013; Adams et al., 2017). On the other hand, cancer patients often experience disproportional loneliness, precipitated by several related factors, such as stigma, undesirable effects of cancer and its treatment, and the fear of recurrence (Kim et al., 2009; Kroenke et al., 2013; Knapp et al., 2014; Mahendran et al., 2020). Caregivers of cancer patients also suffer from a higher level of loneliness when compared to non-caregivers (Ekwall et al., 2005).

DISCUSSION

Human beings did not evolve to be alone (Cacioppo et al., 2014), and exhibit a strong need to belong (Baumeister & Leary, 1995). However, many individuals experience the subjective perception of either quantitative or qualitative deficiencies in personal and social relationships in their lives and feel lonely (Perlman & Peplau, 1981). This feeling of loneliness has been noted in individuals all over the world (Richard et al., 2017; Rico-Uribe et al., 2016; Zhong et al., 2018; van Tilburg & Fokkema, 2018; Cohen-Mansfield et al., 2009; Victor & Bowling, 2012; Yang & Victor, 2011; Stickley et al., 2014; Griffin, 2010; Steed et al., 2007; Tiwari, 2013; Wilson & Moulton, 2010). Studies have reported loneliness in Europe (Yang & Victor, 2011; Rico-Uribe et al., 2016), Asia (Yang et al., 2018; Chokkanathan, 2020) and Africa (Ojembe & Ebe Kalu, 2018). In the US, loneliness has been reported in all age groups (Asher et al., 1984; Cassidy & Asher, 1992; De Jong and van Tilburg, 1999; Victor et al., 2005). One study involving kindergarteners and first graders reported that 12% felt lonely at school (Cassidy & Asher, 1992) while 8.4% of third through sixth graders reported being lonely (Asher et al., 1984). De Jong Gierveld and van Tilburg found that up to 32% of adults over the age of 55 report experiencing loneliness at any given time (De Jong & van Tilburg, 1999). It is also common in the 65+ age group (Victor et al., 2005). A recent study in the US of adults aged 18 and older found that 46 percent reported "sometimes or always feeling alone" (<https://www.cigna.com/about-us/newsroom/studies-and-reports/combatting-loneliness/>).

Loneliness has severe detrimental physical and mental effects on the human body (Richard et al., 2017). Physical ailments linked with loneliness include obesity (Lauder et al., 2006), diabetes (Lauder et al., 2020), elevated blood pressure (Hawley et al., 2006), coronary artery disease (Valtorta, et al., 2018), cognitive decline (Wilson et al., 2007), recurrent stroke (Cacioppo et al., 2014), and insomnia (Cacioppo et al., 2002). It is also associated with premature mortality (Luo et al., 2012). Psychiatric dysfunctions associated with loneliness include depression (Cacioppo et al., 2010), alcoholism (Akerlind & Hörnquist, 1992), suicidal ideation

(Rudatsikira et al., 2007), aggressive behaviors, and impulsivity (Ernst & Cacioppo, 1999; Cacioppo et al, 2014).

Impact of loneliness on cancer

Loneliness exerts several negative effects on cancer (Williams et al., 2009; Jaremka et al., 2014; Nausheen et al., 2010; Adams et al. 2017; Drageset et al. 2013) including increasing its risk (Williams et al., 2009), magnifying the symptoms (Jaremka et al., 2014), accelerating the disease progression (Nausheen et al., 2010), worsening the health-related quality of life (Adams et al. 2017), and decreasing survival (Drageset et al., 2013). The deleterious effects of loneliness on cancer are also influenced by unhealthy lifestyles (Behrens et al., 2018). Lonely people have reduced self-regulation (Hawkley & Cacioppo et al., 2010) and this contributes to the increased prevalence of unhealthy lifestyles noted in these individuals (Stickley et al., 2013; Richard et al., 2017; Algren et al., 2020). Unhealthy lifestyles include physical inactivity (Shiovitz-Ezra & Litwin, 2012), smoking (Christakis & Fowler, 2008), high alcohol intake (Shiovitz-Ezra & Litwin, 2012), having an improper diet (Locher et al., 2005), being overweight/obese (Whisman, 2010), and engaging in risky sex (Torress & Gore-Felton, 2007). Unhealthy lifestyles have a major negative impact on cancer incidence and progression (Khan et al., 2009). Individuals with stronger social connections are less likely to practice poor lifestyles (Samuel et al., 2015). Lonely people are more physically inactive and less likely to exercise (Hawkley et al., 2009; Page & Hammermeister, 1995; Vancampfort et al., 2019; Netz et al., 2013) Physical activity, including exercise, helps prevent several cancers (Physical Activity Guidelines Advisory Committee, 2018), decreases cancer-related symptoms such as fatigue, anxiety, and depression (Schmitz et al., 2019), improves the quality of life (Bourke et al., 2014), and increases survival (Patel et al., 2019). Lonely people tend to smoke more than non-lonely people (Dyal & Valente, 2015; Kobayashi & Steptoe, 2018; Shankar et al., 2011). Cigarette smoke is rich in carcinogens (Secretan et al., 2009), and can cause cancers almost in any bodily part, especially in the lungs (Lee et al., 2012), colon (Botteri et al., 2008), breast (Gaudet et al., 2013), stomach (Ladeiras-Lopes et al., 2008), and uterus/cervix (ICESCC, 2007). Continued smoking in cancer patients leads to poor treatment response, increased treatment-related side effects (NCCDPHP, 2014; Daniel et al., 2009), diminished quality of life (Danson et al., 2016), a higher risk of cancer recurrence (Warren et al, 2019), and an increase in the risk of developing a second primary cancer (Do et al., 2004). Lonely people are more likely to abuse alcohol (Canham et al., 2016). Cancers related to alcohol intake are numerous (Islami et al., 2018), and include those of the esophagus and stomach (Choi et al., 2018; Day et al., 1994), breast (IARC, 2010), colon/rectum (Fedirko et al., 2011), liver (Bagnardi et al., 2015), prostate (Watters et al., 2010), lung (Bagnardi et al., 2015), and skin (Rota et al., 2017). Diet also plays an important role in cancer (Potter et al., 2016). Lonely people are less likely to consume fruits and vegetables and more likely to consume excessive amounts of red meat, processed meat, and junk food (Locher et al., 2005). Greater vegetable and fruit consumption helps prevent cancers of the stomach, esophagus, lung, breast, oral cavity and pharynx, endometrium, pancreas, and colon (Steinmetz & Potter, 1996), while a diet rich in meat and animal products, especially processed meat (hot dogs, bacon, sausages, deli meat) increases the risk of getting cancers of the breast, colon, stomach, and prostate (Chan et al., 2011; Bouvard et al., 2015). A prudent diet also helps reduce many cancer-associated symptoms such as pain and fatigue (Arthur et al., 2014), improves the quality of life in these individuals (Kassianos et al, 2015), and increases survival (Kushi et al., 2012). It also retards the development of second primary cancers in cancer survivors (Murphy et al., 2017).

Loneliness leads to higher (Rotenberg & Flood; 1999) and unhealthy food consumption (Baumeister et al., 2005) and reduced exercise (Hawley et al., 2009), contributing to the increased obesity seen in these individuals (Lauder et al., 2006). Excess body fat is responsible for many cancers (Islami et al., 2018), including cancers of the esophagus (Kubo & Corley, 2006), liver (Larsson & Wolk, 2007), gallbladder (Larsson & Wolk, 2007a), pancreas (Larsson et al., 2007) breast (Feola et al., 2006), stomach (Kubo & Corley, 2006), uterus (Brinton et al., 2007), ovary (Bandera et al., 2016), kidney (Golabek et al., 2016), colon/rectum (Dong et al., 2017), and the meninges (Wiedmann et al., 2013). Obesity also plays a detrimental role in cancer recurrence and the development of second primary cancers (Sang et al., 2016). It is associated with an increase in mortality in cancer patients (Calle et al., 2003). Obesity-related stigma results in lower rate of work hire, lesser promotions, and higher wrongful dismissal - factors that further fuel social isolation (Chen et al., 2012). Lonely people are also more likely to engage in risky sex (Torress & Gore-Felton, 2007). Risky sex promotes sexually transmitted infections (Holmes & Levine, 2004) and some of these can lead to cancer (IARC, 2012). Hepatitis B (Mahale et al., 2019) and hepatitis C (Mahale et al., 2017) infections are associated with liver cancer. Human papillomavirus infection can lead to cervical, anal, vaginal, and penile cancer (Barchitta et al., 2018). Epstein-Barr virus infection is associated with Burkitt lymphoma and Hodgkin lymphoma (Thun et al., 2017). HIV has profound immunosuppressive effects, and this makes it a co-carcinogen for oncogenic viruses, especially the Kaposi Sarcoma virus (Tso et al., 2017). It is estimated that healthy lifestyle habits and preventable screening can prevent a significant number of cancers, including 33% of lung cancers, 42% of breast cancers, 43% of colon cancers, and 20% of prostate cancers (<https://www.nhs.uk/news/cancer/lifestyle-and-cancer-rates/>).

Lonely people are also more depressed than non-lonely people (Cacioppo et al., 2006). Depressive symptoms include low mood, lack of energy, sadness, and insomnia (DSM-V, 2013) which tend to worsen cancer and its treatment-associated symptoms. Co-morbid depression also leads to an increased treatment noncompliance (DiMatteo et al., 2003), a more rapid disease progression (Satin et al., 2009), a further decrease in the quality of life in these patients (Brown et al., 2014), and decreased cancer survivorship (Pinquart & Duberstein, 2010).

Lonely cancer patients are prone to experience more pain, depression, and fatigue than non-lonely individuals with cancer (Jaremka et al., 2013). They are less likely to be compliant with preventive cancer screening (Lagerlund et al., 2014), and preventive vaccinations (Hajek et al., 2014). They may be more likely to be non-compliant with treatment and other beneficial interventions (Swiatoniowska et al., 2019).

Impact of cancer on loneliness

Cancer itself is conducive to the development of loneliness (Wells & Kelly, 2008; Deckx et al., 2014). Cancer-induced loneliness is commonly seen in younger patients, those who are living under deprived circumstances, those treated with chemotherapy or radiotherapy, and those with advanced disease (Dahill et al., 2020). The severity of loneliness rises with increasing time after cancer diagnosis (Deckx et al., 2014). Cancer patients often suffer from a plethora of unpleasant and often disabling symptoms such as anorexia, fatigue, nausea and vomiting, severe pain, and cognitive dysfunction (Kim et al., 2009; Duncan et al., 2009) and these affect social relationships and precipitate or aggravate loneliness (Foster et al., 2009). Cancer patients may also experience loneliness due to personal issues, such as fear of cancer recurrence and premature death, hopelessness, being a burden to others, and a sense of profound loneliness, grief, regret, or embitterment about what has been missed in life (Campbell-Enns & Woodgate, 2015; Vehling &

Kissane, 2018). They also experience several social issues such as feeling that family members and other social acquaintances are not concerned or receptive to discuss their cancer-related concerns (Adams et al., 2015; Adams et al., 2016). Cancer-related stigma is also common, especially in patients whose cancer is attributed to their behavior, for example, smoking in lung cancer (Lebel & Devins, 2008; Knapp et al., 2014). Cancer patients may also harbor a belief that their disease is a deserved punishment (Peters-Golden, 1982). This can further hinder social participation (Adams et al., 2016). Cancer induced negative social expectations, often help sustain the loneliness (Adams et al., 2017). Cancer treatment itself may cause bleeding, bruising, constipation, delirium, diarrhea, edema, fertility problems, alopecia, memory or concentration problems, mouth and throat issues, peripheral neuropathy, sexual concerns, skin and nail changes, and urinary/bladder problems (Kim et al., 2009), and further increase social isolation. The resultant loneliness may aggravate the fatigue, pain, and cognitive dysfunction often experienced by these patients (Jaremka et al., 2014), result in increased treatment noncompliance (DiMatteo et al., 2003), and decrease the quality of life (Adams et al., 2017).

Mechanisms

Loneliness is associated with dysregulation of the hypothalamo–pituitary–adrenal (HPA) axis and altered cortisol activity (Doane et al., 2010) characterized by blunted morning cortisol rise and a flattened diurnal cortisol rhythm (Zilioli et al., 2017). An overactive HPA axis can lead to increased cancer risk and increased cancer progression (Spiegel, 2012). Loneliness also increases the levels of three systemic inflammation biomarkers: interleukin-6 fibrinogen and C-reactive protein (Smith et al., 2020; Nersesian et al., 2018). Inflammation is associated with the development and progression of cancer (Singh et al., 2019). Loneliness also decreases immunity (Walker et al., 2019). An impaired immune system can play a significant role in cancer emergence and progression (Palmer et al., 2018). Though a disturbed autonomic system may also play a role (Gouin et al., 2015), the above three appear to be the main mechanisms as to how loneliness contributes to the development and a detrimental prognosis in cancer (Reiche et al., 2004). A decrease in healthy behaviors adds a plethora of other mechanisms that are associated with cancer initiation or progression (Sinha et al., 1998; Seitz & Stickel, 2007; Patrelli et al., 2009; Seitz & Stickel, 2010; Rock et al., 2012; Berg et al., 2014; Leitzmann et al., 2015; Bortolato et al., 2017).

Therapeutic Interventions

Several therapeutic interventions have been developed to treat loneliness and include antidepressants, neuro-steroids, and oxytocin (Masi et al., 2010). The use of antidepressants in cancer patients is not uncommon and helps other cancer-related symptoms such as pain, fatigue, anorexia, nausea, vomiting and hot flashes (Grassi et al., 2018). Cognitive behavioral therapy has been shown to be beneficial in lonely individuals and helps cancer patients to improve their quality of life (Daniels, 2015). Social support is important for physical and psychological adjustment to cancer and helps reduce chronic loneliness often experienced by these patients and may help improve cancer prognosis (Usta, 2012; Nausheen et al., 2009). Loneliness plays an important role in the practice of healthy lifestyles and the latter is causally associated with cancer prevention and better outcomes (Khan et al., 2010). Practicing healthy lifestyles should also help prevent non-cancerous chronic diseases such as cardiovascular, diabetes, COPD, arthritis, etc. in the pre- and post-cancer diagnosed patients (Elmwood et al., 2013). Besides targeting loneliness,

lifestyle counseling, and modification should also be a major therapeutic target in cancer patients (Hawley & Cacioppo, 2003; Masi et al., 2010; Cleary & Stanton, 2015).

CONCLUSION

Loneliness is pervasive in our society. Cancer is soon expected to topple cardiovascular diseases to become the number one killer in the world. Loneliness plays an important role in increasing the risk of cancer, amplifying the adverse effects, generating a poor response to treatment, increasing the risk of recurrence, increasing mortality, and increasing the development of second primary cancers in cancer survivors. Cancer itself, due to social stigma and other co-morbid factors, can initiate loneliness or exacerbate it. Lonely individuals are less likely to adopt and adhere to healthy behaviors, further increasing the risk of developing cancer, exaggerating cancer-related symptoms, increasing resistance to therapy, promoting recurrences and the development of secondary cancers, and decreasing survival. Due to the increased survival of cancer patients, loneliness related unhealthy lifestyles make them more susceptible to increased morbidity and mortality from other non-cancerous chronic diseases. Both loneliness and cancer cause depression, another deleterious co-morbidity perniciously impacting all phases of cancer. To summarize, loneliness and cancer are bidirectionally and intricately interlinked, with deleterious outcomes.

Acknowledgement: None

Funding: None

Conflict of interest: None

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