

Secondary Risk Reduction Strategies in Breast Cancer Care

C. Steele¹, S. O'Reilly²

1. School of Medicine, University College Cork, Ireland.
2. Department of Medical Oncology, Cork University Hospital, Ireland and Cancer Research@UCC, College of Medicine and Health, University College Cork, Ireland.

Abstract

Over the past three decades breast cancer survival rates have increased in Ireland. This is due to advances in cancer diagnostics and therapeutics. Cure is now anticipated for most newly diagnosed patients. Cancer survivorship however is associated with an increased risk of additional cancers and the development of other non-communicable diseases such as cardiovascular disease. At present, secondary risk reduction strategies are an integral part of cardiovascular disease management. Given the improvements in breast cancer survival, similar strategies should be implemented as part of routine early-stage breast cancer care treatment plan. Herein, we present compelling evidence to support the integration of secondary risk reduction strategies for patients as a standard of care.

Introduction

The World Health Organisation (WHO) has identified cancer as the first or second leading cause of premature death in 134 out of 183 countries worldwide with breast cancer being the number one diagnosis in females.¹ In developed countries an increase in breast cancer survivorship is causing a shift to that of a chronic condition with an estimated 2 million breast cancer survivors in the UK alone by 2040.² Current age standardised breast cancer survival rates in Ireland are 82.9% at five years and 75.1% at ten years, both of which have increased in the past two decades.³

Along with an increase in survivorship, comes the risk of primary or secondary cancer recurrence and the development of other non-communicable diseases such as cardiovascular disease and dementia. Multiple risk factors including; genetics, environment, lifestyle and age are known to contribute to the development of cancer.⁴ In particular, modifiable lifestyle factors such as; increased body fat, low physical activity, poor diet quality, smoking and alcohol intake, have been identified as increasing risk in many cancer diagnosis as well as contributing to poorer outcomes such as increased mortality.^{5,6} The Irish National Cancer Strategy Program 2017-2026, estimates that between 30% to 40% of cancer incidence in Ireland is attributable to modifiable lifestyle and environmental factors alone. The report lists a number of dietary and lifestyle factors including weight reduction and increasing physical activity as targets for primary and secondary disease prevention in Ireland.⁶ Secondary risk reduction strategies are a well-established part of management in other chronic conditions such as cardiovascular disease.⁷ Considering the modifiability of these risk factors there should be greater emphasis placed on lifestyle interventions for cancer survivors with the aim to integrate these services into the Irish breast cancer care treatment pathways.

Obesity

Obesity in breast cancer is linked to an increase severity and risk of treatment related side effects, reduced quality of life and increased mortality.^{8,9} A recent meta-analysis concluded that obese breast cancer survivors are at a 33% increased risk of mortality and 41% increased risk of death from all-causes.¹⁰ Postulated mechanisms include changes in serological markers associated with obesity such as increased levels of insulin, leptin, inflammatory markers, and post-menopausal oestrogen being associated with poorer outcomes.¹¹ Studies have shown that lifestyle-based interventions in breast cancer survivors can lead to weight loss with the efficacy of these interventions greater among patients who were aware of the high risk associated with disease occurrence.^{12,13}

Physical activity

A substantial amount of research suggests that physical activity is protective against several cancers. Reduction in circulating hormone levels, increased steroid hormone metabolism and reduction in inflammation and insulin resistance are proposed to underpin this finding.¹⁴ Physical activity may also reduce cancer risk through reduction in body fat stores. An Irish study conducted by Hickey et al., identified that between 2011-2015 over 1,500 cancer cases and 500 deaths were attributable to inadequate physical activity. They also found that women were disproportionately affected.¹⁵ Inadequate physical activity is a significant modifiable risk factor; it is important that breast cancer survivors are made aware of this risk, and they should also be supported in achieving higher levels of physical activity. Furthermore, another recent Irish publication proposed compelling evidence to support the need for an exercise promotion amongst cancer survivors.¹⁶ Given the impact physical activity has upon breast cancer outcomes a specific secondary risk reduction campaign and service would be advantageous.

Dietary factors

Research suggests that a poor quality diet; low in fruit and vegetables and high in saturated fat and sugar are associated with increased cancer risk.⁵ Consistent with healthy eating dietary guidelines – a diet high in wholegrains, fruit and vegetables and low in processed foods, saturated fats and refined sugar has been suggested to improve prognosis in early breast cancer survivors.¹⁷ A recent study identified that dietary quality was poorer among cancer survivors.¹⁸ A systematic review assessing dietary patterns, mortality and recurrence in cancer survivors concluded that reduction of dietary fat after breast cancer diagnosis was associated with increased relapse free time. Furthermore, the study identified that a high-quality diet may be beneficial for reducing non breast cancer related mortality.¹⁹ This benefit was confirmed in a recent intervention trial where breast cancer survivors, provided with advice for a low-fat diet post diagnosis, had significantly reduced mortality from all-causes.²⁰ The impact of many different dietary components upon immune and metabolic pathways have been implicated as potential mechanisms of decreased disease risk.

Dietary polyphenols, found in seeds, fruits and vegetables, are postulated to alter epigenetic activation of oncogenes and tumour suppressor genes.²¹ Furthermore, a high fibre diet causes an upregulation of butyrate production by the gut microbiome, an increase in butyrate increases favourable epigenetic and immunomodulatory effects.²² Although much more investigation on specific dietary components is required, there is compelling evidence to support the need for accessible and easily implementable healthy eating advice for breast cancer survivors. This should be provided from qualified healthcare practitioners and supported through reliable evidence-based resources.

Smoking and alcohol intake

Alcohol intake is a modest but well documented risk factor for the development of primary breast cancer. Increased lifetime alcohol consumption and heavy episodic drinking amongst moderate lifetime drinkers has been associated with increased risk of breast cancer.²³ The mechanistic role of alcohol in carcinogenesis is complex, involving acetaldehyde and folate metabolism, oxidative stress, and of particular significance in breast cancer, the circulating levels of oestrogen and androgens.²⁴

Smoking has been a long-known risk factor for cancer development. A meta-analysis involving over 400,000 breast cancer survivors concluded that there was a 28% increase in breast cancer-associated mortality in current smokers compared to those who had never smoked. Of particular interest was that mortality in former smokers was the same as those who had never smoked. This finding suggests that breast cancer survivors, who stop smoking, can decrease their risk of dying from breast cancer significantly.²⁵ Furthermore, continued smoking and alcohol consumption in combination post diagnosis increases the risk of secondary recurrence.²⁶ The evidence outlined above identifies that the time of diagnosis of breast cancer is a pivotal moment for lifestyle modification advice and this should be a core focus of secondary risk reduction guidance and clinical practice.

Concluding remarks

Increased body fat, low physical activity, poor quality diet, alcohol and smoking are modifiable risk factors for primary and secondary cancer development. Increasing awareness amongst breast cancer survivors and encouraging engagement to achieve beneficial lifestyle changes is of paramount importance. Furthermore, sufficient awareness and engagement of healthcare professionals in risk reduction strategies is imperative. Modification of lifestyle behaviours in cancer care would be best targeted alongside the Irish National Cancer Strategy program and other national strategies on health and wellbeing. Effective implementation of similar health promotion programs such as Healthy Ireland, the National Physical Activity Plan and The National Obesity Plan would be important. Targeted strategies like that of the Irish Heart Foundation Cardiac Rehabilitation program could be utilised as a blueprint for this urgent public health issue. Research is required to inform local and national guidance on the secondary risk reduction services required and to enable stakeholders to tailor health promotion programs to the needs of this cohort. Information on the current understanding of these modifiable risk factors and acceptability of risk reduction services amongst breast cancer survivors and oncology clinicians would be essential. This research is currently underway at Cork University Hospital.

In summary, the focus in breast cancer care is often on pharmacological prescribing however the weight of evidence supports the importance of lifestyle interventions in parallel for this cohort. As a first step, patients should receive tailored counselling on the importance of improving diet, weight and alcohol reduction, smoking cessation, and increasing physical activity as part of their breast cancer treatment plan. These measures would impact their cancer related morbidity and mortality and favourably improve their risk of cardiovascular disease and dementia risk, the other two leading causes of death in our society.

Declaration of Conflicts of Interest:

None to declare.

Corresponding Author:

C. Steele

School of Medicine,

University College Cork,

Ireland.

E-Mail: clara.steele@umail.ucc.ie

References:

1. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. 2020.
2. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010–2040. *British journal of cancer*. 2012 Sep;107(7):1195-202.
3. National Cancer Registry Ireland. Breast Cancer Survival Statistics 2010-2014 [Available from: <https://www.ncri.ie/data/survival-statistics>. [Accessed April 14th 2021].
4. Pashayan N, Antoniou AC, Ivanus U, Esserman LJ, Easton DF, French D, Sroczynski G, Hall P, Cuzick J, Evans DG, Simard J. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. *Nature Reviews Clinical Oncology*. 2020;17(11):687-705.
5. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, Brauer M, Burnett R, Cercy K, Charlson FJ, Cohen AJ. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The lancet*. 2016; 8;388(10053):1659-724.
6. Department of Health and NPS Office. National Cancer Strategy 2017-2026. Ireland; 2017.
7. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *European journal of preventive cardiology*. 2021 May;28(5):460-95.

8. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast cancer research and treatment*. 2010 Oct;123(3):627-35.
9. Imayama I, Alfano CM, Neuhouser ML, George SM, Smith AW, Baumgartner RN, et al. Weight, inflammation, cancer-related symptoms and health-related quality of life among breast cancer survivors. *Breast cancer research and treatment*. 2013;140(1):159-76.
10. Chan DSM, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies. *Annals of Oncology*. 2014;25(10):1901-14.
11. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *Journal of clinical oncology*. 2002;20(1):42-51.
12. Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. *Obesity reviews*. 2014;15(9):749-68.
13. Harvie M, Pegington M, French D, Cooper G, McDiarmid S, Howell A, et al. Breast cancer risk status influences uptake, retention and efficacy of a weight loss programme amongst breast cancer screening attendees: two randomised controlled feasibility trials. *BMC cancer*. 2019;19(1):1089.
14. de Boer MC, Wörner EA, Verlaan D, van Leeuwen PA. The mechanisms and effects of physical activity on breast cancer. *Clinical breast cancer*. 2017;17(4):272-8.
15. Hickey D, Collins A, Lyng A, McCarthy C. Cancer Incidence and Mortality Due to Inadequate Physical Activity. *Irish Medical Journal*. 2020.113;(10);P199.
16. Watson G, Leonard G. Prescribing exercise for cancer survivors: Time for physicians to become more proactive. *Irish Medical Journal*. 2020;113(2):25.
17. Kwan ML, Weltzien E, Kushi LH, Castillo A, Slattery ML, Caan BJ. Dietary patterns and breast cancer recurrence and survival among women with early-stage breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(6):919-26.
18. Zhang FF, Liu S, John EM, Must A, Demark-Wahnefried W. Diet quality of cancer survivors and noncancer individuals: Results from a national survey. *Cancer*. 2015;121(23):4212-21.
19. Jochems SH, Van Osch FH, Bryan RT, Wesselius A, van Schooten FJ, Cheng KK, et al. Impact of dietary patterns and the main food groups on mortality and

recurrence in cancer survivors: a systematic review of current epidemiological literature. *BMJ open*. 2018;8(2).

20. Chlebowski RT, Aragaki AK, Anderson GL, Simon MS, Manson JE, Neuhouser ML, et al. Association of low-fat dietary pattern with breast cancer overall survival: A secondary analysis of the Women's Health Initiative randomized clinical trial. *JAMA oncology*. 2018;4(10):e181212-e.
21. Carlos-Reyes Á, López-González JS, Meneses-Flores M, Gallardo-Rincón D, Ruíz-García E, Marchat LA, et al. Dietary Compounds as Epigenetic Modulating Agents in Cancer. *Frontiers in Genetics*. 2019;10.
22. O'keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. *Nature reviews Gastroenterology & hepatology*. 2016;13(12):691.
23. White AJ, DeRoo LA, Weinberg CR, Sandler DP. Lifetime alcohol intake, binge drinking behaviors, and breast cancer risk. *American journal of epidemiology*. 2017;186(5):541-9.
24. International Agency for Research on Cancer. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Personal habits and indoor combustions, in *A Review of Human Carcinogens*. . Lyon, France; 2009.
25. Sollie M, Bille C. Smoking and mortality in women diagnosed with breast cancer-a systematic review with meta-analysis based on 400,944 breast cancer cases. *Gland surgery*. 2017;6(4):385-93.
26. Knight JA, Fan J, Malone KE, John EM, Lynch CF, Langballe R, et al. Alcohol consumption and cigarette smoking in combination: A predictor of contralateral breast cancer risk in the WECARE study. *International journal of cancer*. 2017;141(5):916-24.