DOI: 10.1002/efd2.45

COMMENTARY

eFood WILEY

Balancing the scales: Do healthy lifestyle choices offset the colorectal cancer risk of unhealthy choices?

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1 | BALANCING THE SCALES OF COLORECTAL CANCER: CAN HEALTHY LIFESTYLE CHOICES OFFSET THE RISK OF UNHEALTHY CHOICES?

Colorectal cancer (CRC) is the third most diagnosed cancer worldwide and second highest cause of cancer deaths (Sung et al., 2021). CRC prevention research is crucial to reduce its impact on public health and the economy, as its total cost in Europe amounts to €12.2 billion annually (Hofmarcher et al., 2020). Lifestyle and diet play an important role in numerous diseases including CRC (Cena & Calder, 2020), with risk factors including unhealthy diet, sedentary lifestyle, and excess body weight (World Cancer Research Fund, 2018). It is estimated that 54% of CRC cases are preventable through healthy lifestyle changes (Cancer Research UK, 2022a). Lifestyles and diets are variable, and research needs to address how factors interact to influence CRC's cell of origin. Intestinal stem cells (ISCs), marked by expression of *Lgr5,* reside at the base of intestinal crypts and are thought to be the cell of origin (Barker et al., 2009), supporting a bottom-up model of tumorigenesis (Preston et al., 2003). However, the latest work describing cell plasticity (Gil Vazquez et al., 2022; Tian et al., 2011) indicates that differentiated cells, potentially carrying a mutation, further up the crypt can dedifferentiate into ISCs if the ISC pool undergoes trauma (Gil Vazquez et al., 2022). As mutated cells near the crypt surface normally undergo anoikis and are shed into the lumen, this evidence supports a top-down model of CRC initiation that can arise if the ISC pool is depleted by dietary or inflammatory means (Ngo et al., 2022). The idea that environmental factors and inflammation prime cells to initiate tumorigenesis, independent of carcinogen-induced mutagenesis, was recently supported by Swanton et al. (2022). A high-fat diet (HFD) is known to increase inflammation and associated CRC risk, as opposed to exercise and dietary fiber that dampen inflammation and CRC risk (Byrd et al., 2020). Understanding how lifestyle and dietary components may prime the ISC pool and epithelium for tumorigenesis is crucial to understand CRC initiation.

A reduced ISC pool, via healthy lifestyle, may potentially prime progenitor cells to replenish the ISC pool if healthy choices are neglected. While it is beneficial if a healthy lifestyle is maintained resulting in a decreased CRC risk, the temporary adoption of unhealthy lifestyles increases the potential for non-ISCs to dedifferentiate; this can drive rapid expansion of the ISC pool from non-ISC sources which have an increased risk of carrying an oncogenic mutation. Here we discuss this scenario in the context of lifestyle choices that are associated with increased or decreased CRC risk (Figure 1).

2 | HFD AND INCREASED CRC RISK

Obesity is an epidemic, leading to a 30%–70% elevated CRC risk (Mantovani et al., 2018). Therefore, understanding the link between a pro-obesity HFD and CRC is of particular interest. HFD-induced obesity expands the ISC pool and enhances the self-renewal potential of ISCs and progenitor cells, via increased peroxisome

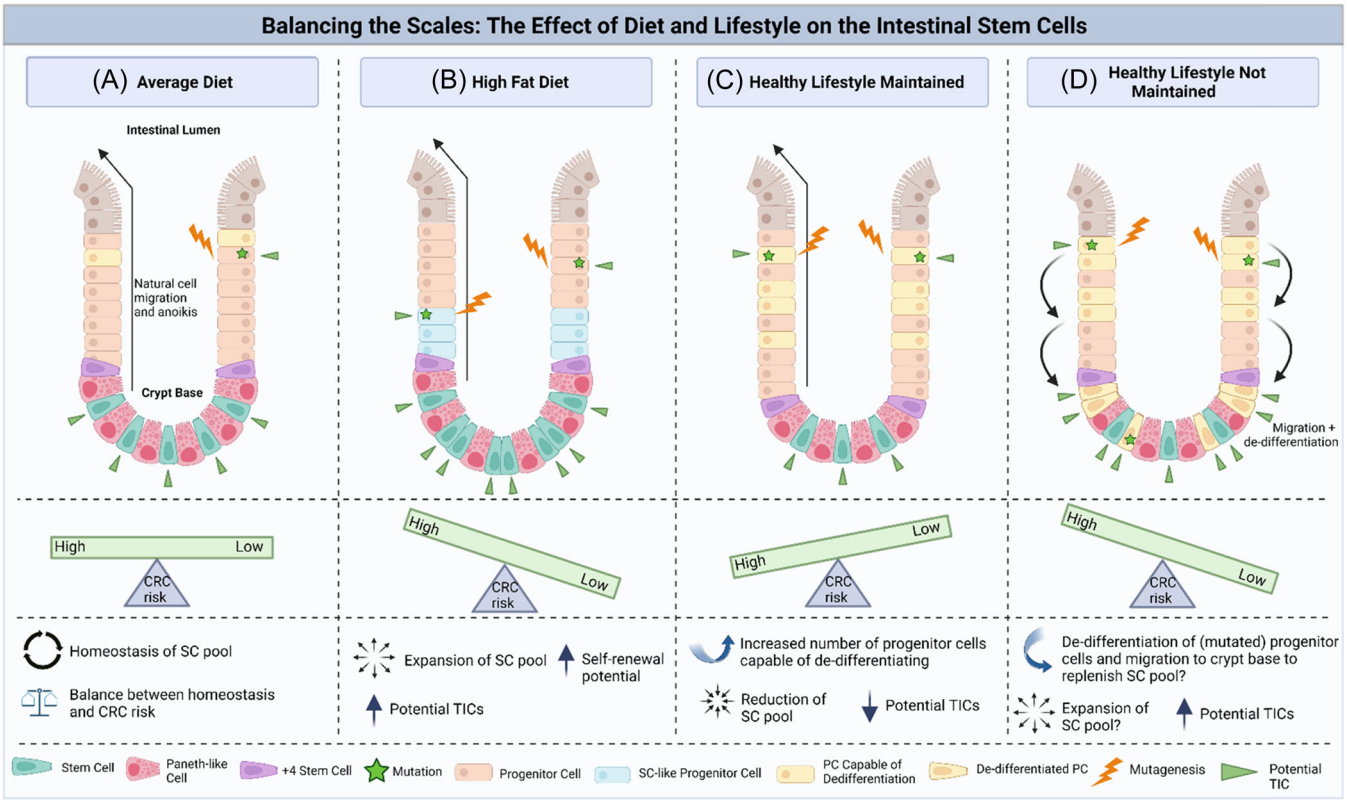

FIGURE 1 Potential effects of different lifestyle factors on the intestinal stem cells (ISCs) and CRC risk. (A) Under normal conditions intestinal cellular homeostasis is maintained by the ISCs. They produce cells that proliferate and differentiate as they migrate up the crypt before being shed, due to anoikis, at the surface. This mechanism prevents the fixation and malignant progression of any cells mutated during this process and underpins the bottom-up model of CRC originating from a mutated ISC. Dietary/lifestyle factors can impact this process, leading to altered CRC risk. (B) An HFD leads to increased numbers of ISCs and increased stemness of PCs, increasing the number of potential tumor-initiating cells and elevating CRC risk. (C) In contrast, a healthy lifestyle requires less ISCs to maintain gut homeostasis, reducing CRC risk. Potentially leading to an increase in the number of PCs capable of dedifferentiating to an ISC to ensure that the ISC pool can be rapidly repopulated in response to ISC injury. (D) However, while a healthy lifestyle reduces CRC risk, a period of adopting an HFD/unhealthy lifestyle may drive the expansion of the ISC pool from PCs. These cells carry a greater risk of harboring an oncogenic mutation resulting in an elevated CRC risk that is disproportionate to the risk associated with an average lifestyle. This report highlights the potential for a greater understanding of the interplay between lifestyle and ISCs is crucial to improve public health advice and support the management of CRC risk. CRC, colorectal cancer; HFD, high-fat diet; PC, progenitor cell; PPAR, peroxisome proliferator-activated receptor; SC, stem cell; TIC, tumor-initiating cell. Created with Biorender.com.

proliferator-activated receptor (PPAR) signaling, affecting intestinal homeostasis and facilitating tumorigenesis (Beyaz et al., 2016; Mana et al., 2021). Higher ISC numbers increase the chance of a cell acquiring an oncogenic mutation. Increased progenitor cell stemness supports the top-down model of CRC initiation, an alternative to the ISC cell of origin hypothesis. HFD-induced PPAR activation promotes tumorigenesis via a shift towards fatty acid oxidation (FAO) metabolism, with increased fatty acid uptake and breakdown (Mana et al., 2021). Potentially this plays a role in the association between exercise and reduced CRC risk. Physical exercise decreases FA uptake, stimulates lipolysis, providing fuel for energy utilization from different sources, either FAs transported in the circulation or from lipolysis of muscle triglyceride stores (Mika et al., 2019).

More holistic research is needed to understand the balance between healthy and unhealthy lifestyle components. Can exercise counterbalance HFD's effects, specifically on ISCs? An interesting study by Ju (Ju et al., 2008) found that exercise in HFD-fed mice decreased tumor number. Conflictingly Baltgalvis et al. (2009) found that moderate intensity exercise in HFD-fed mice had no effect on polyp or adenoma development. The HFD increased inflammation and immunosuppression may be dampening the effect of exercise. These conflicting results may be due to differences in exercise duration and intensity, with mice in Ju et al. (2008)'s study running further and for longer periods of time. Therefore, higher intensity of exercise may be crucial to prevent polyp formation in an HFD context. Future research should focus on this complicated and variable relationship between diet, exercise, and energy production on ISCs and CRC initiation, rather than individualistic studies. Consumption of an HFD doesn't necessarily mean the absence of healthy dietary components associated with reduced CRC risk.

3 | EXERCISE AND REDUCED CRC RISK

Robust evidence links exercise and reduced CRC risk through animal model studies, clinical trials, and meta-analysis (Amirsasan et al., 2022). Physically active individuals have a 24%–40% reduced CRC risk. Exercise reduces intestinal polyp and tumor formation in CRC mouse models (Colbert et al., 2000, 2003, 2006; Ju et al., 2008; Mehl et al., 2005). This preventative effect is due to numerous mechanisms, indirectly through decreasing obesity and directly via modulation of proliferation, apoptosis, and inflammation (Amirsasan et al., 2022). Acute aerobic exercise reduces cancer cell proliferation in vitro by reducing DNA damage via interleukin-6 (Orange et al., 2022). This preventative effect of exercise on tumor development correlates with an increase in intestinal flora (Ren et al., 2022). Understanding the mechanisms through which exercise reduces CRC risk is crucial, with its effects on the ISCs warranting further investigation. Does exercise reduce tumor burden through a reduced ISC pool, decreasing the number of cells capable of initiating tumourigenesis? What effect would fluctuations in exercise have on the ISC pool?

4 | DIET AND REDUCED CRC RISK

Numerous dietary components, such as fiber and fruit, are associated with reducing CRC risk (World Cancer Research Fund, 2018), including black raspberries (BRBs; May et al., 2022). BRB-supplementation decreases ISC number and self-renewal potential, protecting against tumorigenesis. It would be interesting to see if BRB-supplementation could counteract HFD's effect, reducing ISC population and cancer risk. ISC reduction following BRBs supplementation is associated with increased *Ascl2* expression, (May et al., 2022) which regulates epithelial cell dedifferentiation (Murata et al., 2020). Increased *Ascl2* expression may be compensatory for the decreased ISC pool, with $Ascl2^{+ve}$ non-ISCs capable of migrating to the ISC compartment, replacing lost $Lgr5^{+ve}$ ISCs. It would be interesting to explore whether a drop in BRB-supplementation would expand $Ascl2^{+ve}$ cells within the ISC compartment, contributing to the top-down model of CRC initiation. It is important to understand for correct public health information whether "healthy" dietary components, when depleted, potentially promote tumorigenesis rather than protect against it.

Cancer Research UK recommends 30 g of fiber per day to reduce CRC risk (Cancer Research UK, 2022b). However, whether dietary fiber is protective against CRC is controversial, as studies show conflicting evidence (Donohoe et al., 2014). Butyrate is a short-chain fatty acid produced via bacterial fermentation of dietary fiber within the intestinal lumen and is the colonocytes' main energy source (Carretta et al., 2021; Salvi & Cowles, 2021). As the majority of butyrate is absorbed by colonocytes, there exists a natural butyrate gradient within crypts, being the lowest at the crypt base (Kaiko et al., 2016). It is believed that crypt morphology has evolved to protect ISCs from butyrate's antiproliferative effects. Butyrate suppresses ISC and progenitor cell proliferation as it functions as a histone deacetylase (HDAC) inhibitor (Kaiko et al., 2016). Butyrate fluctuates with eating patterns; therefore, we should explore how this affects the ISCs. Does butyrate reduction confer ISC plasticity, allowing stem and progenitor cells to proliferate and expand the pool?

Numerous studies show butyrate as a tumor suppressor (Donohoe et al., 2014; Li et al., 2017; Xiao et al., 2018); however, there are also reports of butyrate functioning in an oncogenic manner (Bultman & Jobin, 2014). Antibiotic treatment in CRC mouse models attenuates intestinal polyp formation via decreased butyrate production by intestinal bacteria (Belcheva et al., 2014). Butyrate may drive carcinogenesis via promoting intestinal cancer cell proliferation. Further establishment of the role of butyrate and the microbiome is needed to explain these discrepancies and explore how natural butyrate fluctuations contribute to its effect on ISCs.

Butyrate's effect on obesity is also controversial (Yu et al., 2019). Butyrate supplementation in HFD-fed mice prevented body weight gain, counteracting HFD pro-obesity effects via decreasing PPAR activity and expression, switching from lipogenesis to lipolysis (den Besten et al., 2015; Lu et al., 2016). However, does butyrate diminish HFD-associated increased stemness? Oppositely butyrate can be obesity-promoting via increasing lipid synthesis from acetyl-CoA (Liu et al., 2018). Yu et al. (2019) first explored the combined effect of butyrate and exercise within different dietary contexts, showing that butyrate and exercise, independently and in combination, protect against HFD-induced obesity. However, the combination was the least effective. Perhaps this is due to excess butyrate production, as exercise increases intestinal butyrate-producing bacteria, reversing the protective effects of exercise. The variability of lifestyles and diet on fitness and plasticity of ISCs and progenitor cells would explain why dietary components' roles in CRC are controversial and difficult to establish. Different lifestyle factors can be tumor-promoting or preventing, but it's important to understand the balance between them. Would consuming a fiber-rich diet or exercise counteract an HFD increase in ISCs?

5 | CONCLUSION AND PERSPECTIVE

Lifestyles are variable, with differences in diet, exercise, and microbiome varying widely between individuals. Thus, exploring their effect on ISCs and CRC is

complicated. It is important that we remember this variability and that our models and studies reflect it. With an increase in obesity and HFD consumption, it's crucial that we understand how these balance alongside healthy lifestyle choices, as well as how lifestyle fluctuations influence ISCs and CRC initiation. Understanding how an unhealthy diet increases CRC risk will support public health advice and produce nutraceutical agents to prevent CRC or augment existing therapies. To address this, it is important to understand how diet, microbiome, epigenome, and environment impact ISCs, cellular plasticity, and pre-malignant ISCs.

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REFERENCES

Amirsasan, R., Akbarzadeh, M., & Akbarzadeh, S. (2022). Exercise and colorectal cancer: Prevention and molecular mechanisms. *Cancer Cell International*, *22*(1):247.

Baltgalvis, K. A., Berger, F. G., Peña, M. M. O., Davis, J. M., & Carson, J. A. (2009). The interaction of a high-fat diet and regular moderate intensity exercise on intestinal polyp development in Apc Min/+ mice. *Cancer Prevention Research*, *2*(7), 641–649.

Barker, N., Ridgway, R. A., van Es, J. H., van de Wetering, M., Begthel, H., van den Born, M., Danenberg, E., Clarke, A. R., Sansom, O. J., & Clevers, H. (2009). Crypt stem cells as the cells-of-origin of intestinal cancer. *Nature*, *457*(7229), 608–611.

Belcheva, A., Irrazabal, T., Robertson, S. J., Streutker, C., Maughan, H., Rubino, S., Moriyama, E. H., Copeland, J. K., Surendra, A., Kumar, S., Green, B., Geddes, K., Pezo, R. C., Navarre, W. W., Milosevic, M., Wilson, B. C., Girardin, S. E., Wolever, T. M. S., Edelmann, W., … Martin, A. (2014). Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. *Cell*, *158*(2), 288–299.

den Besten, G., Bleeker, A., Gerding, A., van Eunen, K., Havinga, R., van Dijk, T. H., Oosterveer, M. H., Jonker, J. W., Groen, A. K., Reijngoud, D. J., & Bakker, B. M. (2015). Short-chain fatty acids protect against high-fat diet-induced obesity via a PPARγ-dependent switch from lipogenesis to fat oxidation. *Diabetes*, *64*(7), 2398–2408.

Beyaz, S., Mana, M. D., Roper, J., Kedrin, D., Saadatpour, A., Hong, S. J., Bauer-Rowe, K. E., Xifaras, M. E., Akkad, A., Arias, E., Pinello, L., Katz, Y., Shinagare, S., Abu-Remaileh, M., Mihaylova, M. M., Lamming, D. W., Dogum, R., Guo, G., Bell, G. W., … Yilmaz, Ö. H. (2016). High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. *Nature*, *531*(7592), 53–58.

Bultman, S. J., & Jobin, C. (2014). Microbial-derived butyrate: An oncometabolite or tumor-suppressive metabolite? *Cell Host & Microbe*, *16*(2), 143–145.

Byrd, D. A., Judd, S. E., Flanders, W. D., Hartman, T. J., Fedirko, V., Agurs-Collins, T., & Bostick, R. M. (2020). Associations of novel dietary and lifestyle inflammation scores with incident colorectal cancer in the NIH-AARP diet and health study. *JNCI Cancer Spectrum*, *4*(3):pkaa009.

Cancer Research UK. (2022a). Bowel cancer statistics. [cited September 13, 2022].

Cancer Research UK. (2022b). Wholegrains, fibre and cancer risk. [cited September 21, 2022].

Carretta, M. D., Quiroga, J., López, R., Hidalgo, M. A., & Burgos, R. A. (2021). Participation of short-chain fatty acids and their receptors in gut inflammation and colon cancer. *Frontiers in Physiology*, *12*, 662739.

Cena, H., & Calder, P. C. (2020). Defining a healthy diet: Evidence for the role of contemporary dietary patterns in health and disease. *Nutrients*, *12*(2):334.

Colbert, L. H., Mai, V., Tooze, J. A., Perkins, S. N., Berrigan, D., & Hursting, S. D. (2006). Negative energy balance induced by voluntary wheel running inhibits polyp development in APCMin mice. *Carcinogenesis*, *27*(10), 2103–2107.

Colbert, L. H., Davis, J. M., Essig, D. A., Ghaffar, A., & Mayer, E. P. (2000). Exercise and tumor development in a mouse predisposed to multiple intestinal adenomas. *Medicine & Science in Sports & Exercise*, *32*(10), 1704–1708.

Colbert, L. H., Mai, V., Perkins, S. N., Berrigan, D., Lavigne, J. A., Wimbrow, H. H., Gregory Alvord, W., Haines, D. C., Srinivas, P., & Hursting, S. D. (2003). Exercise and intestinal polyp development in APCMin mice. *Medicine & Science in Sports & Exercise*, *35*(10), 1662–1669.

Donohoe, D. R., Holley, D., Collins, L. B., Montgomery, S. A., Whitmore, A. C., Hillhouse, A., Curry, K. P., Renner, S. W., Greenwalt, A., Ryan, E. P., Godfrey, V., Heise, M. T., Threadgill, D. S., Han, A., Swenberg, J. A., Threadgill, D. W., & Bultman, S. J. (2014). A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumorigenesis in a microbiota- and butyrate-dependent manner. *Cancer Discovery*, *4*(12), 1387–1397.

Gil Vazquez, E., Nasreddin, N., Valbuena, G. N., Mulholland, E. J., Belnoue-Davis, H. L., Eggington, H. R., Schenck, R. O., Wouters, V. M., Wirapati, P., Gilroy, K., Lannagan, T. R. M., Flanagan, D. J., Najumudeen, A. K., Omwenga, S., McCorry, A. M. B., Easton, A., Koelzer, V. H., East, J. E., Morton, D., … Leedham, S. J. (2022). Dynamic and adaptive cancer stem cell population admixture in colorectal neoplasia. *Cell Stem Cell*, *29*(8), 1213–1228.e8.

Hofmarcher, T., Lindgren, P., Wilking, N., & Jönsson, B. (2020). The cost of cancer in Europe 2018. *European Journal of Cancer*, *129*, 41–49.

Ju, J., Nolan, B., Cheh, M., Bose, M., Lin, Y., Wagner, G. C., & Yang, C. S. (2008). Voluntary exercise inhibits intestinal tumorigenesis in Apc(Min/+) mice and azoxymethane/dextran sulfate sodium-treated mice. *BMC Cancer*, *8*, 316.

Kaiko, G. E., Ryu, S. H., Koues, O. I., Collins, P. L., Solnica-Krezel, L., Pearce, E. J., Pearce, E. L., Oltz, E. M., & Stappenbeck, T. S. (2016). The colonic crypt protects stem cells from microbiota-derived metabolites. *Cell*, *165*(7), 1708–1720.

Li, Q., Ding, C., Meng, T., Lu, W., Liu, W., Hao, H., & Cao, L. (2017). Butyrate suppresses motility of colorectal cancer cells via deactivating Akt/ERK signaling in histone deacetylase dependent manner. *Journal of Pharmacological Sciences*, *135*(4), 148–155.

Liu, H., Wang, J., He, T., Becker, S., Zhang, G., Li, D., & Ma, X. (2018). Butyrate: A double-edged sword for health? *Advances in Nutrition*, *9*(1), 21–29.

Lu, Y., Fan, C., Li, P., Lu, Y., Chang, X., & Qi, K. (2016). Short chain fatty acids prevent high-fat-diet-induced obesity in mice by regulating G protein-coupled receptors and gut microbiota. *Scientific Reports*, *6*, 37589.

Mana, M. D., Hussey, A. M., Tzouanas, C. N., Imada, S., Barrera Millan, Y., Bahceci, D., Saiz, D. R., Webb, A. T., Lewis, C. A., Carmeliet, P., Mihaylova, M. M., Shalek, A. K., & Yilmaz, Ö. H. (2021). High-fat diet-activated fatty acid oxidation mediates intestinal stemness and tumorigenicity. *Cell Reports*, *35*(10):109212.

Mantovani, A., Dauriz, M., Byrne, C. D., Lonardo, A., Zoppini, G., Bonora, E., & Targher, G. (2018). Association between non-alcoholic fatty liver disease and colorectal tumours in asymptomatic adults undergoing screening colonoscopy: A systematic review and meta-analysis. *Metabolism: Clinical and Experimental*, *87*, 1–12.

May, S., Greenow, K. R., Higgins, A. T., Derrick, A. V., Taylor, E., Pan, P., Konstantinou, M., Nixon, C., Wooley, T. E., Sansom, O. J., Wang, L. S., & Parry, L. (2022). Modification of diet to reduce the stemness and tumorigenicity of murine and human intestinal cells. *Molecular Nutrition & Food Research*, *66*, e2200234.

Mehl, K. A., Davis, J. M., Clements, J. M., Berger, F. G., Pena, M. M., & Carson, J. A. (2005). Decreased intestinal polyp multiplicity is related to exercise mode and gender in ApcMin/+ mice. *Journal of Applied Physiology*, *98*(6), 2219–2225.

Mika, A., Macaluso, F., Barone, R., Di Felice, V., & Sledzinski, T. (2019). Effect of exercise on fatty acid metabolism and adipokine secretion in adipose tissue. *Frontiers in Physiology*, *10*, 26.

Murata, K., Jadhav, U., Madha, S., van Es, J., Dean, J., Cavazza, A., Wucherpfennig, K., Michor, F., Clevers, H., & Shivdasani, R. A. (2020). Ascl2-dependent cell dedifferentiation drives regeneration of ablated intestinal stem cells. *Cell Stem Cell*, *26*(3), 377–390.e6.

Ngo, P. A., Neurath, M. F., & López-Posadas, R. (2022). Impact of epithelial cell shedding on intestinal homeostasis. *International Journal of Molecular Sciences*, *23*(8):4160.

Orange, S. T., Jordan, A. R., Odell, A., Kavanagh, O., Hicks, K. M., Eaglen, T., Todryk, S., & Saxton, J. M. (2022). Acute aerobic exercise-conditioned serum reduces colon cancer cell proliferation in vitro through interleukin-6-induced regulation of DNA damage. *International Journal of Cancer*, *151*(2), 265–274.

Preston, S. L., Wong, W. M., Chan, A. O., Poulsom, R., Jeffery, R., Goodlad, R. A., Mandir, N., Elia, G., Novelli, M., Bodmer, W. F., Tomlinson, I. P., & Wright, N. A. (2003). Bottom-up histogenesis of colorectal adenomas: Origin in the monocryptal adenoma and initial expansion by crypt fission. *Cancer Research*, *63*(13), 3819–3825.

Ren, J., Guo, B., Sui, H., Chen, J., Zhang, L., Lv, C., & Li, B. (2022). The effects of aerobic exercise on the intestinal tumors and flora of the Apc(Min/+) mouse. *Clinical and Translational Oncology*, *24*(2), 305–318.

Salvi, P. S., & Cowles, R. A. (2021). Butyrate and the intestinal epithelium: Modulation of proliferation and inflammation in homeostasis and disease. *Cells*, *10*(7):1775.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249.

Swanton, C., Hill, W., Lim, E., Lee, C., Weeden, C. E., Augustine, M., Chen, K., Kuan, F. C., Marongiu, F., Rodrigues, F., Cha, H., Jacks, T., Luchtenborg, M., Malanchi, I., Downward, J., Carlsten, C., Hackshaw, A., Litchfield, K. R., DeGregori, J., & Jamal-Hanjani, M. (2022). LBA1 mechanism of action and an actionable inflammatory axis for air pollution induced non-small cell lung cancer: Towards molecular cancer prevention. *Annals of Oncology*, *33*, S1413.

Tian, H., Biehs, B., Warming, S., Leong, K. G., Rangell, L., Klein, O. D., & de Sauvage, F. J. (2011). A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. *Nature*, *478*(7368), 255–259.

World Cancer Research Fund. (2018). *Diet, nutrition, physical activity and colorectal cancer*. Continuous Update Project Expert Report 2018 [cited September 13, 2020].

Xiao, T., Wu, S., Yan, C., Zhao, C., Jin, H., Yan, N., Xu, J., Wu, Y., Li, C., Shao, Q., & Xia, S. (2018). Butyrate upregulates the TLR4 expression and the phosphorylation of MAPKs and NK-κB in colon cancer cell in vitro. *Oncology Letters*, *16*(4), 4439–4447.

Yu, C., Liu, S., Chen, L., Shen, J., Niu, Y., Wang, T., Zhang, W., & Fu, L. (2019). Effect of exercise and butyrate supplementation on microbiota composition and lipid metabolism. *Journal of Endocrinology*, *243*(2), 125–135.

How to cite this article: Williams, N. G., & Parry, L. (2022). Balancing the scales: Do healthy lifestyle choices offset the colorectal cancer risk of unhealthy choices? *eFood*, 3, e45. https://doi.org/10.1002/efd2.45