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Mechanism of how skipping breakfast promotes the development of gastrointestinal tract cancers: A review

Zhihan Lin[1,5,†], Henghui Zeng[2,6,*,†], Tiancheng Chen[3,7], Zengtao Li[4,8]

[1]Department of Clinical Nutrition, Shanghai Jiaotong University, Shanghai, 200240, China
[2]Department of Food Science and Technology, Beijing Normal University-Hong Kong Baptist University United International College, Zhuhai, 519087, China
[3]School of Medicine, Shanghai Jiaotong University, Shanghai, 200025, China
[4]Ningbo Huamao International School, Ningbo, 315100, China

[5]henrylzh@sjtu.edu.cn
[6]s230013036@mail.uic.edu.cn
[7]luckyhopefan@sjtu.edu.cn
[8]jack.li@nbhis.com
*corresponding author
[†]These authors contributed equally to this work and should be considered co-first authors.

Abstract. Gastrointestinal cancers are cancer types with high morbidity and mortality rates around the globe. Meanwhile, skipping breakfast has become more and more common among people. Researches showed that frequently skipping breakfast led to a greater risk of gastrointestinal tract cancers. Researches hitherto are dispersed. Circadian rhythm can be disrupted by skipping breakfast, leading to the dysfunction of DBP, which regulates the circadian rhythm oscillation of P450 Family 7 Subfamily A Member 1 (CYP7A1). Cholesterol 7α-hydroxylase is coded by CYP7A1, controlling the synthesis of bile acids. Bile acids show their toxicological effect by producing ROS and secondary bile acids, also risk factors for gastrointestinal cancers. Circadian rhythm can also lead to abnormal clock genexpression. Thus, it results in accelerated cell proliferation and diabetes, which contributes to gastrointestinal tract cancers. From the aspect of hormones, skipping breakfast may give rise to abnormal fluctuation of various hormone levels, including Ghrelin, peptide YY, cholecystokinin, Leptin, and insulin. They may contribute to cancer progression via their receptors, proliferation, apoptosis of tumor cells, overexpression of certain proteins, or obesity. Current researches are not flawless. Issues that exist include a lack of clinical trials, relatively weak association, and a dearth of comparison, and these issues should be figured out in future research. The review aims to render a systematical summary of the detailed mechanisms of how omitting breakfast may contribute to gastrointestinal tract cancers and raise the awareness of people to have breakfast regularly.

Keywords: Gastrointestinal cancers, Breakfast skipping, Circadian rhythm, Hormone.

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1. Introduction

Breakfast is the most important of the three meals. Nowadays, breakfast is habitually skipped. Fujiwara, etc., showed that 32.4% of the 3110 subjects sometimes or never eat breakfast, while the figures for skipping lunch and dinner were 5.59% and 6.20%, respectively [1]. Skipping breakfast may do harm to people's health [2]. Besides leading to obesity and diabetes, it is positively related to cancer mortality [3]. Because of the promotion of the development of cancer, in addition to individual misery, neglecting breakfast also threatens society in that it puts a heavy burden on the social security system. In 2015, up to $190.2 billion was spent on treating cancer in the U.S., while the spending on colorectal cancer shared the largest proportion. Apart from the tremendous population skipping breakfast and huge treatment costs, the death toll of gastrointestinal tract cancers is also high. At the same time, cancers have been the second leading cause of death throughout the world. Colon and rectum cancer, along with stomach cancer, are two of the top three major cancer deaths by type in 2021, giving rise to respectively 1.04 million and 954,374 deaths. The death caused by cancer led to the great loss of the labor force.

Based on the skimmed articles and done researches, several pathways may explain how skipping breakfast leads to gastrointestinal tract cancers, which include gastric cancer, small intestine cancer, colon cancer and rectal cancer. Firstly, skipping breakfast may result in abnormal bile acid synthesis, which promotes the synthesis of active oxygen and nitrogen, damaging the cell's mitochondria and DNA, weakening the apoptosis ability, and further leading to colon cancer [4]. Secondary bile acids (SBAs) are also to blame for the development of cancer because they or their metabolites are carcinogenic. Secondary, skipping breakfast was linked to abnormal expression of the clock gene, thus contributing to diabetes progression, which is speculated to increase the risk of developing gastrointestinal tract cancers [5-8]. The gene expression anomaly may be associated with cancer progression directly as well. Thirdly, gastrointestinal tract cancers may be caused by breakfast skipping through affecting several hormones, including Ghrelin, peptide YY, Leptin, cholecystokinin, and insulin. So far, scientists have conducted abundant surveys on the mechanisms of skipping breakfast and gastrointestinal tract cancers. Nevertheless, the findings were isolated and the result needed to be summarized concisely. The review aims to render a systematical summary of the detailed mechanisms of how omitting breakfast may contribute to gastrointestinal tract cancers and raise the awareness of people to have breakfast regularly.

2. Methods

For databases, PubMed and Science Direct are the major resources of the essays. The articles published before 2024 are screened based on the title and abstract and skimmed. Since the review focus on the relationship between skipping breakfast and the development of gastrointestinal tract cancers, 'Skip breakfast AND bile acid', 'bile acid AND gastrointestinal cancers', 'skip breakfast AND hormone', 'ghrelin AND cancer', 'insulin AND gastrointestinal cancers', 'insulin AND skip breakfast', and 'skip breakfast AND clock gene' were keywords and searched, rather than using single words or phrase. Similar terms, including 'breakfast skipping,' 'neglecting breakfast,' and 'no breakfast,' were also included while searching.

3. Possible Mechanisms

3.1. Skipping breakfast leads to gastrointestinal cancers through BAs

Breakfast skipping is related to the abnormal synthesis of BAs, which may contribute to the generation of ROS and SBAs, further contributing to the development of gastrointestinal cancers. Figure 1. shows each steps of how skipping breakfast lead to gastrointestinal cancers through BAs.

3.1.1. Skipping breakfast contributes to DBP dysfunction

The circadian clock confers a 24-hour structure on processes, including gene expression and behaviors. In turn, the circadian clock regulates metabolic processes and physiological activities. He, etc., showed that functional circadian rhythms affect bile acid synthesis in mice [9]. Similarly, irregular eating, such as breakfast skipping and late dinners, can also impact bile metabolism in humans through disruption of

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circadian homeostasis [10]. D-box Binding Protein (DBP) acts as the transcription factor of CYP7A1 (P450 Family 7 Subfamily A Member 1), thereby regulating its transcription. DBP regulates the circadian rhythm of CYP7A1 through binding to D-box elements on the promoter of CYP7A1, thereby increasing the expression level of CYP7A1. DBP transcription activator follows strict circadian rhythms and is widely expressed in the liver (Lavery & Schibler, 1993); its dysfunction disrupts the timely regulation of CYP7A1, which codes a rate-limiting enzyme, called Cholesterol 7α-Hydroxylase, that catalyzes the conversion of cholesterol to bile acids [11]. Yamajuku pointed out that irregular eating patterns may also disrupt several clock genes, including DBP, that further perturb the circadian oscillation of CYP7A1, and the delayed expression of CYP7A1 contributes to a higher plasma bile acid level [12].

3.1.2. BAs and gastrointestinal cancers

Bile acids (BAs) are responsible for several important physiological functions in the liver and the intestine. Since 1939, bile acids have been regarded to be associate with the development of cancers. The exposure of gastrointestinal cells to repeated high bile acids concentration is highly related to the development of gastrointestinal cancers [13]. According to Bernstein, a higher level of hydrophobic BAs may increase the risk of developing stomach cancer, small bowel cancer, and colon cancer in the human body [4]. Generating reactive oxygen and nitrogen species (ROS/RNS) and the secondary bile acids (deoxycholic acid (DCA) and lithocholic acids (LCA)) are the two important mechanisms of how BAs lead to gastrointestinal cancers.

BAs show the cytotoxic effects of increasing the generation of ROS and RNS [4]. Exposure to BAs involves multiple pathways, including destroying the cell membrane and mitochondria, which may contribute to the synthesis of ROS/RNS. BAs contain both hydrophilic and hydrophobic groups, allowing them to function as detergents. Because of this characteristic, BAs can insert into the lipid bilayer of the cytomembrane, changing the membrane stability, which further leads to a stronger osmosis. In this case, the physical barrier is weakened, allowing more ROS/RNS and pathogens to enter the cell. After BAs damage the cytomembrane, the ROS may further destroy the organelles in a cell by oxidizing the amino acid residues of protein and lipids in organelles, further promoting the synthesis of ROS [14]. The increased number of ROS and RNS may contribute to the damage of DNA, which may result in the risk of gene mutation [15]. Oxidative stress is one of the important pathogenesis of gastrointestinal cancers. The principle is that DNA's nitrogenous bases and deoxyribose may react with ROS, changing the hereditary information. The increased risk of developing cancer is related to reduplicate DNA damage through mutating cancer suppressor genes.

Cell apoptosis is an important mechanism to stand up to the development cancers. However, if the cells live in the environment with agents that induce apoptosis, like BAs, they may develop into apoptosis-resistant cells. These cells grow more easily than normal cells with the presence of BAs, which leads to the formation of a field of apoptosis-resistant cells [16]. In such a field, repeated exposure to BAs further contributes to DNA damage, which may result in malignant tumors [15].

3.1.3. SBAs and gastrointestinal cancers

The synthesis of deoxycholic acid (DCA) and lithocholic acids (LCA), two kinds of secondary bile acids (SBAs), which are the products of primary bile acids through 7α-dehydroxylation, are the two most quantitatively important and most physiologically significant conversion of bile acids in humans [17].

DCA, a monohydroxybile acid, impacts intestinal permeability and has a genotoxic effect on colorectal cancer (CRC) development because of its hydrophobicity [18]. The overgrowth, migration, and invasion of CRC may be strengthened by DCA [19]. The metabolism of BAs has an impact on the growth of intestinal bacteria, including *Bacteroides fragilis, Bacteroides vulgatus, Clostridium perfringens,* and *Clostridium* [20]. *Bacteroides* are related to gastrointestinal cancers. Their populations in colons with CRC are more plentiful than normal ones, occupying most of the CRC biological film [20,21]. Ndousse-Fette, etc., pointed out that the proportional abundance of *Bacteroides* was positively related to DCA [22]. Kantilal etc. and [24] Kakiuchi etc. found that the expression of cyclooxygenase

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(COX)-2 may be changed by enterotoxigenic *B. fragilis* (ETBF), and the overexpression of the enzyme may result in inflammation, abnormal cell proliferation, inhibition of apoptosis and increased metastatic potential of cancer [23,24]. BFT, a zinc-dependent metalloprotease toxin, is also generated by ETBF [25]. BFT may contribute to intestinal inflammation, which further promotes cancer formation [26]. Similarly, DCA alters barrier function in the colon, causing increased antigen and bacterial uptake, which contribute to the development of intestinal inflammation and cancers [27]. Lithocholic Acid (LCA), a kind of dihydroxy bile acid, also worked as an endogenous CRC promoter as DCA [28,29]. [30] explained that LCA can generate ROS, which may lead to the residence of apoptosis and cell proliferation in the Gastrointestinal compartment, further contributing to the development of gastrointestinal cancers. In addition, the expression of HLA antigen on the surface of colon cancer cells may be inhibited by LCA, which leads to the failure of immune surveillance [31]. Besides, Halvorsen and Raufman proposed that the expressions of matrix metalloproteinase (MMP) genes were increased by LCA, and the expressions contribute to cancer cell invasion and tumor metastasis [32,33].

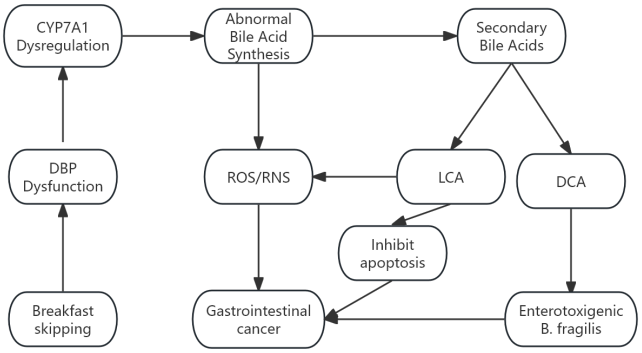


Figure 1. How skipping breakfast leads to gastrointestinal cancers through BAs.

3.2. Clock gene

Clock gene is a set of genes that regulate the circadian clock in human body. The CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle ARNT-like 1) are the core genes in the loop regulating the circadian clock. The dimer of the protein they encoded acts like a starter, which activates the expression of Per (Period genes) and Cry (Cryptochrome genes). Per and Cry proteins can accumulate and repress CLOCK and BMAL1 [34]. REV-ERBα (Reverse erythroblastosis virus α) are also activated by the CLOCK and BMAL1, inhibiting their activity [35]. In contrast, activated RORα (Retinoic acid receptor–related orphan receptor α) promotes the transcription of the two genes [36]. Other genes encoding proteins like AMPK (Adenosine 5'-monophosphate-activated protein kinase) also significantly function in circadian clock control. The whole processes of how the clock gene contributes to cancer are shown in Figure 2.

3.2.1. Clock gene and cancer cell proliferation

Researches have shown that skipping breakfast may correlate with clock gene expression disorder. The expression pattern of clock genes was found to be changed if subjects did not have breakfast, which suggests that the circadian clock may be disrupted [5]. The circadian clock disorder can be a promoter of cancer progression, which results in cancer cells' reproduction under the regulation of circadian clock genes. Filipski proposed that tumor growth was accelerated in mice with disrupted circadian rhythms [37].

Per1, a member of Per genes, plays an important role in cancer development, and its expression declines when breakfast is skipped [5]. It is found to be inhibited in human gastric cancer cells, and lower Per1 expression can be linked to more life-threatening cancer and worse survival [38]. The mechanism may be that the down-regulation of Per1 results in increasing levels of cyclinD and cyclinE,

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which facilitate cancer cells' proliferation in its cell cycle, and low Per1 levels may reduce cancer cells' sensitivity to apoptosis [39].

3.2.2. Clock gene, diabetes, and cancer

Another way clock gene dysfunction may contribute to gastrointestinal tract cancers is that it results in circadian misalignment and thus disrupts normal metabolism in the human body. This may lead to diabetes, which adds to the risk of gastrointestinal tract cancers [40]. Morris, etc., indicated that circadian misalignment causes decreased glucose tolerance and increased 24-h glucose and insulin levels, indicating that the disorder possibly leads to diabetes [41]. Impaired glucose tolerance is associated with abnormal glucagon secretion, the main mechanism of diabetes genesis.

AMPK's function in circadian clock regulstion is controlling the level of phosphorylate and degrading cryptochrome [42]. AMPK activates the Sirt1 (Silent information regulator 1) by adjusting the NAD+ level [43], and insufficient Sirt1 is correlated with the dysfunction of the pancreas, including decreasing the number of PP cells and suppression of insulin secretion [44]. Therefore, irregular AMPK expression can result in diabetes because it can cause impairment in blood sugar regulation and function of β-cell. The expression of AMPK encoding genes is found to drop in subjects skipping breakfast, suggesting that skipping breakfast may be a promoter of diabetes and increase the risk of gastrointestinal tract cancers [5].

The expression pattern of BMAL1 is also disrupted when breakfast is skipped. The gene is the core part of the circadian clock, and research showed that their disruption can be critical in diabetes genesis [45]. Researches on BMAL1's function in human body metabolism found that overexpression of BMAL1 can increase the β-cell function and enhance the expression of genes regulating insulin secretion, showing the BMAL1's effect on pancreas function [46]. In conclusion, BMAL1 disruption can be a risk factor for diabetes and, thus, a risk factor for gastrointestinal tract cancers.

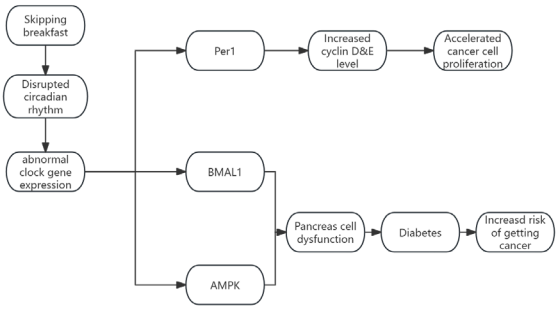


Figure 2. How skipping breakfast leads to gastrointestinal cancers through clock genes.

3.3. Hormonal Mechanisms

Skipping breakfast interactions on a variety of hormones inside the body, including but not limited to Ghrelin, peptide YY (PYY), cholecystokinin (CCK), Leptin, and insulin, as shown in Figure 3.

3.3.1. Ghrelin

Ghrelin is a hormone whose level changes dramatically throughout the day. Its concentration peaks when people fast or before people eat and plummets once people ingest food, reaching the bottom about an hour after a meal. Therefore, Ghrelin is also known as an appetite motivator. In this way, the ghrelin level remains high for the whole morning if a person skips breakfast. Ghrelin is characterized as the ligand of the growth hormone secretagogue receptor, or GHSR. Evidence has been found that in addition to its original function in adjusting appetite, the expression of GHSR may be associated with cancer progression through its regulatory function [47]. It has been observed that Ghrelin and GHSR are produced in many tissues, including the stomach, small intestine, and large intestine. Cancer studies

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have found the expression of Ghrelin and GHSR in gastric cancer and colorectal cancer with the aid of IHC or RT-PCR [48]. The findings suggest that Ghrelin may be a critical factor in cancer progression.

The effect Ghrelin has on cancer cell proliferation is disputable. In the past decade, Ghrelin was reported to induce colon cancer cell proliferation through the GHS-R/Ras/PI3K/Akt/mTOR axis [49]. Additionally, T. Waseem, etc. elucidated the role of the ghrelin axis in colorectal cancer using RT-PCR and Western blot analyses [50], demonstrating that ghrelin expression is enhanced in malignant colorectal cells and promotes colorectal malignancy by advancing stage of the tumor through an autocrine/paracrine mechanism [50]. Whereas other researchers concluded that Ghrelin could suppress the growth of cells. It has been observed in the PC3 cell line that a lower range of ghrelin concentrations (from 10 to 100 pM) promoted cell growth. In contrast, a higher concentration (1μm) had the opposite effect, curbing the proliferation of cells [51].

Regarding regulating apoptosis, a few studies have shown that Ghrelin inhibits apoptosis through different mechanisms. According to Yang, M. et al., Ghrelin protects against apoptosis [52]. In the context of the rat PC-12 pheochromocytoma cell line derived from an adrenal medullary neoplasm, Ghrelin has been demonstrated to exert a protective effect against apoptotic processes. This protective mechanism is mediated by inhibiting apoptosis signal-regulating kinase 1 (ASK1) activation. Ghrelin induces the expression of heat shock protein 70 (Hsp70), which is known to confer cellular resilience against stress-induced apoptosis. On the contrary, Belloni, A. S, etc. reported a significant elevation in the baseline apoptosis rate within the SW-13 and NCI-H295 adrenocortical carcinoma cell lines and in primary aldosterone cells [53]. Therefore, the researchers posited that Ghrelin could exert beneficial anti-neoplastic activities through its pro-apoptotic effects through its pro-apoptotic effects. What is more, Ghrelin may also contribute to cell migration and invasion. Ghrelin treatment is observed to increase cell migration rate and stimulate cell invasion depending on its dose [54]. A study found that ghrelin-induced invasion and migration in cells are facilitated by activating the PI3K/Akt pathway, which is known to augment cell motility and invasive capabilities [55].

3.3.2. Peptide YY

PYY regulates appetite and energy homeostasis, controls food intake and body weight by inhibiting gastric emptying, and reduces postprandial nutrient absorption. Skipping breakfast may reduce PYY concentration, as it increases after a meal. According to research, PYY was superior up to 30 minutes after consuming breakfast, compared with breakfast skipping [56]. Another research showed that women who had breakfast exhibited 50-90% higher concentrations of PYY throughout the test period ($P = 0.001$) [57]. Apart from its function linked with satiety, PYY is also concerned with preventing cancer. A decreased expression of PYY may be relevant to the development and progression of colon adenocarcinoma. PYY plays a significant role in multiple aspects of cancer from regulation of cell growth to potential therapeutic applications [58].

3.3.3. Cholecystokinin

Along with PYY, Cholecystokinin (CCK) also increases after a meal. It is the major Hormone responsible for gallbladder contraction and pancreatic enzyme secretion. CCK is produced by I cells in the duodenum and jejunum of the small intestine in response to the presence of fats, proteins, and amino acids in the intestinal lumen. CCK has been implicated in the regulation of satiety and appetite, contributing to the sensation of fullness after a meal. Skipping breakfast may reduce the gastrointestinal tract's demand CCK, potentially affecting the activation of CCK receptors and the subsequent signal transduction process. Many studies have found that CCK receptors have a close correlation with cancer, especially colorectal cancer [59-61]. Compared with para carcinoma tissues, tumor samples showed overexpression of CCK2R ($P = 0.028$), and patients with CCK2R overexpression had a significantly lower chance of surviving diseases. Evidence from animal models and tumor cell lines in vitro suggests that the CCK-2 receptor may contribute to developing esophageal and gastric adenocarcinomas [61].

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3.3.4. Leptin

A study found that leptin concentrations tended to be higher ($P = 0.08$) in women who skip breakfast compared to breakfast eaters [57]. Leptin is a 16-kDa multifuncional peptide hormone released by adipose tissue that helps maintain body weight long-term. It achieves this by regulating hunger by providing the sensation of satiety. Leptin is one of the most important adipokines related to obesity, a risk factor for colorectal cancer [62-64]. Data from clinics and experiments have indicated the absence of the leptin axis as a promotor to the development and progression of tumors, along with a descend in the efficacy of cancer treatments [65]. Many studies suggested that the overexpression of Leptin correlated with tumor progression [66,67].

Erratic leptin signaling and mutations in the leptin gene are correlated with an increased risk of obesity and colorectal cancer [68]. Leptin may suppress T cells' reactivity by influencing tumor cells' behavior and the tumor microenvironment's characteristics [69]. Furthermore, Leptin indirectly boosts the effectiveness of MDSCs within the tumor microenvironment, a collection of varied immature myeloid cells that have gathered due to changes in the normal process of blood cell development. These cells consist of the granulocytic and monocytic ones. The leptin-induced enhancement of MDSCs is facilitated by the cytokine IFN-γ, which is generated in response to Leptin and modulates the activity of the immune checkpoint molecule PD-L1, potentially inducing T cell apoptosis [70]. The binding of leptin receptors to Leptin promotes the expression of proteins against apoptosis and hypoxia inducible factor-1α (HIF-1α), which propels the proliferation and migration of cancer cells [71]. Leptin may also be involved in tumor evasion and metastasis through different mechanisms, including fibroblasts such as Vascular Endothelial Growth Factor (VEGF) and Tumor-Associated Macrophages (TAMs) [72].

3.3.5. Insulin

Insulin is responsible for maintaining blood sugar balance and regulating the development of cells. Skipping breakfast may lead to hyperinsulinemia, which contributes to cancer development. Skipping breakfast may increase overall average blood glucose in a day, contributing to hyperglycemia and further promoting tumor cell growth. [73] also purposed that hyperglycemia increases the mortality of colorectal cancer. The mechanism is thata highblood glucose levels providevides sufficient fuel to cancer cells, accelerating their proliferation. In order to regulate the high blood glucose content, more insulin is generated, leading to insulin resistance. In this case, even more insulin is synthesized, which contributes to hyperinsulinemia. Insulin regulates cell proliferation and metabolism by binding the receptor on the cell surface. When bound, insulin activates the Mitogen-Activated Protein Kinase (MAPK) signal pathways, which are essential for regulating cell proliferation. Due to the excess insulin, the signal pathway is frequently actived, which may cause problems. Firstly, overactivation of MAPK may lead to overquick cell proliferation, which is a risk factor for the development of cancer. In addition, frequent expression of MAPK may inhibit apoptosis. The inactivation of apoptosis is regarded as a key dysregulatory process in the development of most cancers [74]. The mutated cells fail to be cleaned out, creating favorable growing conditions for cancer cells. The mechanisms explain why gastric cancer cells grew larger with insulin than without insulin.

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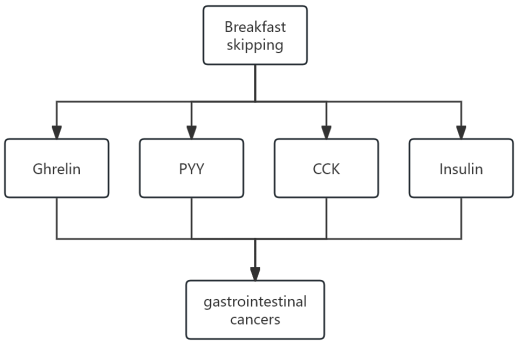


Figure 3. How skipping breakfast leads to gastrointestinal cancers through hormones.

4. Discussion

There are few systematic reviews assessing the mechanism of how skipping breakfast contributes to gastrointestinal cancers. This review covers gene and hormone aspects, and research about the negative impacts of skipping breakfast is included, allowing possible mechanisms to be summarized as comprehensively as possible. Besides, the review strings the dispersive research and theories together into complete logic chains, explaining each step of the mechanism. In addition, since the review has covered several possible mechanisms on how skipping breakfast contributes to gastrointestinal cancers, people who are not familiar with this field can have a brief understanding through the review, and researchers may get some inspiration from this research orientation.

There are several issues worth reflecting on. For BAs pathway, although enough research shows the logical relationship of each adjacent step, there needs to be an article gathering these steps together, making the review argument not powerful and convincing enough. An obvious visual limitation is that the association between skipping breakfast and CYP7A1 is not strong enough. DBP is one of the direct factors that influence CYP7A1, and the direct regulators also include DEC2, and REV-ERB α/β. LXRα, HNF4α, DEC2, E4BP4, and PPARα are also the regulators of CYP7A1 [75]. DEC2 was stated to have no significant function on the mechanism [76]. Whether LXRα, HNF4α, REV-ERBα/β, E4BP4, and PPARα can regulate CYP7A expression through skipping breakfast, remain unclear. If the remaining genes are studied and stated to contribute to CYP7A1 oscillation by skipping breakfast, the logic of the mechanism can be strengthened. Besides CYP7A1, how big breakfast skipping's impact on SBAs remains unclear or has not been directly confirmed by a study since the researches are either qualitative experiments or only looks into the relationship between SBAs and gastrointestinal tract cancers, in which the factor of whether skipping breakfast or not is excluded. The review is not confident enough to claim that the difference on SBAs levels caused by breakfast skipping contributes to gastrointestinal tract cancers, unless direct control experiments measuring the SBAs levels after skipping breakfast are done and some statistics analyzing correlation between the difference in SBAs levels and the incidence probability of gastrointestinal tract cancers are made. Cyclin D and cyclin E promote cell proliferation. When Per1 expression is inhibited, the level of cyclin D and cyclin E increases. That means Per1 is a promoter of csuppoell proliferation and can contribute to cancer progression, supported by experiments. However, the down-regulation of Per1 caused by skipping breakfast can be associated with cancer development, but whether it is enough to cause the genesis of gastrointestinal tract cancers in healthy individuals needs to be confirmed. AMPK and BMAL1 are important genes for clock gene regulation and can regulate the function of the pancreas. The two genes express abnormally if breakfast is skipped. Then, β-cells and PP cells are impaired, and insulin secretion decreases, which is the cause of diabetes. This means that dysfunction of AMPK and BMAL1 is associated with diabetes, which adds to the risk of gastrointestinal cancer, according to statistical data. More data showing the correlation between skipping breakfast and clock gene expression are needed to support. The change in Ghrelin and leptin levels with skipping breakfast is insignificant ($\square = 0.08$). The impact of Ghrelin on cancer cell

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proliferation is debatable and requires further research. In addition, there is a divergence in research regarding Ghrelin's role in apoptosis, necessitating additional investigation. The association between skipping breakfast and PYY lacks direct evidence; existing studies show an increase in PYY levels after breakfast, with no specific research indicating a decrease in PYY levels when skipping breakfast. Moreover, there is limited direct evidence regarding the effect of skipping breakfast on CCK, and the connection between CCK and CCK receptors is unclear. While there are animal model studies for CCK, clinical research is lacking. The link between Leptin and colorectal cancer (CRC) through obesity is indirect, and the evidence may not be strong enough to support it. Last but not least, there is relatively little research on gastric cancer, which may be related to its incidence rate. The mechanisms are not fully understood, and the influence of some hormones on colorectal cancer may not apply to gastric cancer. Scientists discovered that excess insulin in the human body could lead to abnormal cell proliferation. However, it remains to be looked into whether the cancer is caused by insulin resistance in diabetes or only by excess insulin and whether it promotes cancer or directly contributes to it. Furthermore, scientists still need to determine whether some types of cancer, such as gastrointestinal cancer, or all cancers could be influenced by excess insulin and the extent to which these have been affected. Other than that, the specific range of insulin levels in the patient's blood and related issues, such as the patient's body weight and other underlying medical conditions, remain to be investigated. In addition, how a patient's genetic background, such as type-1diabetes and environmental factors such as different eating habits, affect the relationship between abnormal insulin levels and cancer also requires further research.

As argued in the text, skipping breakfast has become increasingly prevalent, which is not a healthy habit. This phenomenon maybe explained by several subjective and objective factors. Firstly, the pace of life is quickened, which is unavoidable and reasonable. In addition, there are also changes in young people's health awareness, which is worrying and less reasonable. People don't think or realize that skipping breakfast has a negative impact on their health, especially under the influence of emerging dietary trends such as intermittent fasting, breakfast skipping is believed to help control weight or improve health. However, there is no strong evidence supporting this idea. In fact, research shows that omitting breakfast makes little difference in energy consumption. That means breakfast fasting has no weight control benefits, and experiments show the same result [40]. This review summarizes the possible mechanisms of how skipping breakfast may induce gastrointestinal tract cancers. More research should be done to determine how skipping breakfast may contribute more clearly to the development of gastrointestinal tract cancers. The review aims to make people aware of the risk of skipping breakfast on developing gastrointestinal tract cancers, thus suggesting that people have regular breakfast every day and adopt a healthy lifestyle.

5. Conclusion

At the gene level, skipping breakfast may break the biological clock and contribute to circadian rhythm oscillation. DBP, the direct regulator of CYP7A1, is sensitive to circadian rhythm oscillation. CYP7A1 codes cholesterol 7α-hydroxylase, and its higher expression promotes cholesterol 7α-hydroxylase synthesis. Higher cholesterol 7α-hydroxylase then lead to higher BAs level. BAs show their toxicological effects by generating ROS, LCA, and DCA, which contribute to the development of gastrointestinal cancers. In addition, skipping breakfast results in disrupted clock gene expression. The disorder of clock gene expression leads to gastrointestinal tract cancers in two ways: one way is that it affects the cell cycle, resulting in abnormal proliferation of cells; the other way is that it cause the dysfunction of genes critical to sugar metabolism and results in increased risk of diabetes, which is a promoter of cancer. In the hormonal section, Ghrelin, PYY, CCK, Leptin, and insulin are mentioned as possible related Hormones to the occurrence of gastrointestinal tract cancers. They may contribute to cancer progression via their receptors, proliferation, apoptosis of tumor cells, overexpression of certain proteins, or obesity.

Acknowledgments

Zhihan Lin and Henghui Zeng are the co-first authors.

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