CHAPTER

8

Colorectal Cancer Prevention by Wheat Consumption: A Three-Valued Logic – True, False, or Otherwise?

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INTRODUCTION

Modern science is permeated by any kind of analysis that relies on breaking something down into primary components. Thus, the method itself can be called "decomposable" in order to establish differences between entities.[1] More data concentrating on primary components would be helpful in achieving easier interpretation of investigated problems. This interpretation needs to be understood by using a language which is based upon primary logic and then mathematics. Looking through evidence from different medical investigations, it is not easy to infer a robust conclusion. "Simple" logic has been changing to a more sophisticated one that makes the interpretation more difficult to reach. The results from medical investigations very often cannot be interpreted with the use of bivalent logics such as classical sentential or Boolean logic, which provide only "true" and "false" alternatives. A three-valued logic appears to be a system in which there are three values indicating true, false, and an indeterminate third value.[2,3] More data are more difficult to interpret clearly, and therefore the answer should be positioned as one of the three-valued entities. We have this complicated situation in interpretation of collected data in the field of the preventive action of nutrients against malignant disease.

COLORECTAL CANCER: EPIDEMIOLOGY AND ETIOLOGY

Nutrients are substances in food that are primarily responsible for providing an energy source to run the system of a living organism independently of its structural organization. Humans are heterotrophs who must obtain their energy and nourishment from organic molecules manufactured by other organisms. Additional value in preserving health, in terms of preventing metabolic diseases and cancer, can be derived from eating "well-tailored" foods. Some nutrients in everyday foods, such as wheat, rye, and other grains, may be useful as strong preventive factors against disease, thus having clinical utility.

Another important part of the living system in the gut is the interaction between the intestinal microbiota and the central nervous system. Ingestion of *Lactobacillus ramnosus* is responsible for regulation of emotional behavior via changes of function in brain GABA (gamma-aminobutyric acid) receptor expression. GABA is the main central nervous system inhibitory neurotransmitter, and is significantly involved in regulating many physiological and psychological processes. Changes in GABA functions are implicated in the pathogenesis of anxiety and depression, which very often exist comorbidly with functional bowel disorders. Consumption of *Lactobacillus ramnosus* in experimental mice reduced the expression of GABA receptors (GABA $_{A\alpha 2}$ at the level of mRNA) in the prefrontal cortex and amygdala with its increase in the hippocampus. The molecular events could be interpreted as important in reducing stress-induced corticosterone and anxiety- and depression-related behavior.[4] Moreover, accumulated experimental data have shown that colonization of the gut microbiota impacts mammalian brain development and subsequent adult behavior.[5] Bidirectional signaling between the gastrointestinal tract and the brain requires neural, hormonal, and immunological mechanisms. The gut–brain axis is a term coined to show how both systems are functionally responsible

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for maintaining the homeostasis of a living organism. Functional analysis of the gut microbiota in relation to the pathology of obesity, autism, and gastrointestinal diseases has been reported, and appears to have an increasing role in understanding many other abnormal conditions, hopefully including cancer.[6]

Colorectal cancer is the third most frequent cancer in men and the second in women. Male incidence rates appear greater than female rates for both proximal and distal cancers. Incidence rates declined by 2.9% per year during the period 1998–2001. This socially positive result comes from increased screening and polyp removal, which inhibits the progression of polyps to cancers. The mortality rate is similar in men and women, and is the fourth commonest cause of cancer death, which is the result of a better prognosis than more common cancers. Mortality rates from colorectal cancer have continued to decline in both men and women over the past 15 years at the level of 1.8% annually. Despite progress in screening, staging, and better treatments, over 35% of diagnosed patients with colorectal cancer die within 5 years. Only 40% of patients with colorectal cancer are diagnosed at a localized stage, when the rate of survival at 5 years is 90%.[7–10]

Management of colorectal cancer is based on surgery in most cases. For cancers that have not spread, surgical removal is often curative. A permanent colostomy is rarely needed for colon cancer, but a little more frequently required for rectal cancer. For rectal cancer, aside from surgery, chemotherapy alone or in combination with radiation therapy has been used successfully for many years. In colon cancer, other than surgery, chemotherapy used in an adjuvant setting or for palliation is considered as a mainstay in the treatment of such patients. In both cancers, rectal and colon, new treatment strategies have been approved since the beginning of the 21st century. Targeted therapy for colorectal cancer is available in clinical practice worldwide. There have been investigations regarding drugs that inhibit angiogenesis (the most developed strategy in the field of monoclonal antibodies and small molecules), with bevacizumab approved for the treatment of metastatic colorectal cancer, and EGFR (epidermal growth factor receptor) inhibitors such as cetuximab and panitumumab (both monoclonal antibodies) accepted for treating metastatic colorectal cancer with the expression of K-ras wild type.[11]

Colorectal cancer usually has a silent course without alarming signs and symptoms in its early stages. Therefore, a screening procedure should be helpful. For a clinically experienced physician, rectal bleeding, blood in the stool, a change in bowel habits, and cramping pain in the abdomen provide adequate signs and symptoms to suspect colorectal cancer. Risk factors are playing an increasing role in early detection of colorectal cancer. The primary risk factor for colorectal cancer is age, with more than 90% of cases diagnosed in patients older than 50 years. Risk is increased by a personal or family history of colorectal cancer and/or polyps, or a personal history of inflammatory bowel disease. Epidemiological investigations have revealed other risk factors to be smoking, alcohol consumption, physical inactivity, and a diet high in saturated fat and/or red meat with a low intake of fruits and vegetables. On the other hand, data have been reported focusing on the use of estrogen and non-steroidal anti-inflammatory drugs that may reduce colorectal cancer risk.[12]

Stools are a reservoir of many compounds, including indigestible parts of food, and many chemical substances, such as fecapentaenes, 3-ketosteroid, and heterocyclic amines, that are produced by the interaction of digestion and food products. It has been estimated that 10^{14} bacteria of hundreds of different species are colonized in the colon. Bacteria have indirect carcinogenic actions in the colon; they deconjugate and reduce bile acids, which further become active substances that promote cell proliferation and growth of adenomas.[13] Secondary bile acids (deoxycholic acid, lithocholic acid, 12-ketolithocholic acid) along with other fecal substances are responsible for the initiation of colorectal carcinogenesis. On the other hand, increased fiber intake in the form of wheat bran or cellulose may reduce the production and excretion of mutagens in stools.[14]

Fecapentaenes are characterized by highly potent mutagenic activity originating from intestinal bacterial production. High performance liquid chromatography (HPLC) analysis enables detection of at least eight forms of fecapentaene-like substances occurring in human stools. Two geometric isomers, fecapentaene-12 and fecapentaene-14, are present in paramount concentrations in the feces (21.7% of total), within fecalpentaene levels ranging from 5 μg to 6 mg/kg feces. Fecapentaenes are mutagens found in human feces that have direct genotoxic effects on colon epithelial cells. Fecapentaene-12 is considered a prototype substance that causes DNA single strand breaks, sister chromatid exchanges, and mutations in cultured human fibroblasts.[15–17]

Bile acids are associated with the digestion of fat. The presence of bile acids correlates with fat consumption, which is a known risk factor for colorectal cancer by activation of the AP-1 transcriptional factor associated with the promotion of malignant transformation in normal epithelial colon cells. Cholecystectomy is a surgical procedure that can result in high levels of bile acids in the cecum and ascending colon which might lead to increased frequency of right-sided colon cancer.[18,19]

Among the other significant etiologic factors, meat intake appears to have a critical role in the development of colorectal cancer. Cooking meats at high temperatures has long been considered a crucial factor in carcinogenesis, mainly regulated by heterocyclic amines. Thus it is

thought that methods of red meat preparation and frequency of intake can be correlated with the prevalence not only of colorectal cancer but also of distal colorectal adenomas.[20,21]

It has been accepted that the human diet is too calorie-dense, with high animal fat, sugar (mostly refined carbohydrates) and alcohol contents. Despite divergent results of studies, in experimental studies positive results can be achieved, and in clinical trials results are very often inconclusive; current recommendations for decreasing the risk of colorectal cancer include dietary changes such as increased plant food intake with consumption of whole grains, vegetables, and fruits, and reduced intake of red meat.[22,23]

SCREENING FOR COLORECTAL CANCER

Cancer screening appears to have a crucial role in achieving clinical benefits at the social level. This goal is very practical, assuming detection of cancer at an early stage when it is treatable and curable. The screening procedure should lead to the early detection of asymptomatic or unrecognized malignant disease by the use of acceptable, inexpensive tests or examinations in a large number of individuals. The main aim of such a screening test is to reduce the morbidity and mortality from a particular cancer among the persons screened.[24] Several cancers are suitable for screening because of their substantial morbidity and mortality; their high prevalence in a preclinical state when detection is possible; the availability of a known treatment that can be applied in an early stage of cancer; and the availability of a good screening test characterized by accepted sensitivity and specificity, low cost, and little direct harm to a given subject. A short assessment of screening tests makes it easy to define cancers that could be suitable for intervention – namely, breast, cervix, colon and rectum, prostate, and other cancers important from the social standpoint.[25]

Patients diagnosed with localized colorectal cancer have a 90% 5-year survival rate.[26] Colorectal cancer mortality could be reduced both by early diagnosis and by cancer prevention using several methods, including polypectomy. Screening tests that can detect either cancer or adenomatous polyps are highly welcome.[27,28] The screening tests pursuing colorectal cancer can be divided in two broad categories: structural tests, and stool/fecal-based tests.[29]

A structural test is a tool for detection (e.g., radiologic imaging), or for detection and removal of adenomatous polyps by the use of an endoscopic instrument. An endoscopic examination may typically be a colonoscopy or a flexible sigmoidoscopy. Colonoscopy allows examination of the entire large bowel with removal of polyps in one session, but requires sedation of the patient. Therefore, this medical procedure is considered to be the current "gold standard" for the assessment of screening procedures. Polypectomy is also considered to be able to reduce colorectal cancer incidence by 50%.[30,31] Flexible sigmoidoscopy does not need sedation and careful bowel preparation, but it seldom crosses the boundary beyond 60 cm and is thus limited to examination of the end of the descending part of the colon tract. When examination by flexible sigmoidoscopy is positive in the form of multiple polyps larger than 1 cm, such patients should be referred for colonoscopy because of the higher propensity for adenomatous polyps to be located in the proximal part of the colon tract.[32] Virtual colonoscopy is an interesting diagnostic procedure that relies on computed tomographic colonography and has a radiation exposure dose of 10 mSv. This radiologic procedure may be useful for the detection of larger polyps measuring 10 mm or more. A positive finding with virtual colonoscopy requires a colonoscopy to remove the polyps.[33,34] A double-contrast barium enema has a marginal role in colorectal screening, and is typically used as an alternative for patients who cannot undergo colonoscopy.

Fecal tests are responsible for the detection of indications of cancer in stool samples, such as occult blood or changes in DNA from cancer cells. Currently, there are two fecal occult blood tests available; guaiac-based, and immunochemical. The guaiac-based tests have cancer detection rate of 37–79%. The range of detection is dependent on the size of the colon lesions (smaller lesions are less frequently detected) and non-human heme in food. The fecal immunochemical test directly detects human globin within hemoglobin, and does not require dietary restrictions. However, the sensitivity (25–72%) and specificity (59–97%) are also very wide.[35,36] A stool DNA test relies on detection of the presence of known DNA alterations that occur during colorectal carcinogenesis in tumor cells appearing in the stool. The first investigative attempt showed that K-ras mutation could be a marker of exfoliated tumor cells mixed in the stool.[37]

The incidence of colorectal cancer varies, and depends upon many factors due to both nature and nurture. The average risk of developing colorectal cancer emerges in humans at the age of 50 years and more, without a history of adenoma, colorectal cancer itself, inflammatory bowel disease, or family history predisposition. An increased risk of developing colorectal cancer embraces a personal history of adenomatous polyps, and factors defined above in the average risk group. Finally, high-risk syndromes are defined when a family history of Lynch syndrome or polyposis syndromes is precisely characterized. Table 8.1[38–48] shows representative results of large clinical studies screening individuals at an average risk of colorectal cancer development.

TABLE 8.1 Screening of Individuals at Average Risk of Colorectal Cancer: Representative Large Studies

Age at Entry	Number of Patients	Screening Method	Periodicity	Randomization (yes, no)	Outcome	Reference
I. STRUCTURAL SCREENING TEST						
50–90 years (mean 64 years)	2,412,077 patients	Complete colonoscopy	Not given	No	For every 1% increase in complete colonoscopy rate, the hazard of death from colorectal cancer decreased by 3%.	Rabeneck *et al.*[38]
60.3 ± 8.7years	7882 patients	Colonoscopy	ND	No	Adenomatous polyps were detected in 23.5% of patients; hyperplastic lesions were detected in 21.4% of patients; advanced neoplasms were detected in 5.2% of patients; strong relationships between withdrawal times (less than 6 minutes vs 6 minutes and longer) and lesion-detection rates were observed.	Barclay *et al.*[39]
56.7 ± 7.5 years	2436 patients	Screening colonoscopy at baseline and rescreening colonoscopy in those who had no neoplastic lesions in baseline colonoscopy	Rescreening after 5 years	No	Patients with no adenomas in screening were rescreened after 5 years; no cancer was found on rescreening colonoscopy; the risk of an advanced adenoma did not differ significantly between persons with no polyps at baseline and those with hyperplastic polyps at baseline (1.1% vs 2.0%), respectively; rescreening interval of 5 years or longer after a normal colonoscopic examination is sufficient.	Imperiale *et al.*[40]
45–91 years (mean 66 years)	261 patients	Rigid sigmoidoscopy	Sigmoidoscopy within 10 years before cancer diagnosis	No	Screening by sigmoidoscopy can reduce mortality from cancer of the rectum and distal colon (0.41 risk reduction [95% CI, 0.25–0.69]); screening once during 10 years can be efficacious as more frequent.	Selby *et al.*[41]
55–64 years	170,432 patients	Flexible sigmoidoscopy	Only once	Yes	Incidence of colorectal cancer in people attending screening was reduced by 33% (95% CI 0.67, 0.60–0.76) and mortality by 43% (95% CI 0.57, 0.45–0.72); the numbers that needed to be screened to prevent one colorectal cancer diagnosis or death were 191 (95% CI 145–277) and 489 (95% CI 343–852), respectively.	Atkins *et al.*[42]
Not given	4181 patients	CT colonography	Not given	No	CT colonography revealed, for large polyps (>1 cm) per patient, average sensitivity 93% (95% CI: 73–98%) and specificity 97% (95% CI: 95–99%); sensitivity and specificity decreased to 86% (95% CI: 75–93%) and 86% (95% CI: 76–93%), respectively, when the threshold was lowered to include medium polyps (0.6–1 cm). Data were inconclusive for small polyps (<0.6 cm) due to heterogeneity. Of 150 cancers, 144 were detected (sensitivity 95.9%; 95% CI: 91.4–98.5%).	Halligan *et al.*[43]
Mean age of patients enrolled in included studies was 61.9 years	6393 patients	CT colonography		No	Sensitivity of CT colonography for detection of polyps <6 mm was 48% (95% CI: 25–70%); for polyps 6–9 mm, 70% (95% CI: 55–84%) and 85% (95% CI: 79–91%) for large polyps >9 mm. Specificity was homogenous: 92% (95% CI: 89–96%, polyps <6 mm), 93% (95% CI: 91–95%, polyps 6–9 mm), and 97% (95% CI: 96–97%, for polyps >9 mm).	Mulhall *et al.*[44]

Colonography group:57.0 ± 7.2 years; Colonoscopy group:58.1 ± 7.8 years	3120 patients (colonography group); 3163 patients (colonoscopy group)	CT colonography (CTC group); optical colonoscopy (OC group)	Once	No	Advanced neoplasia was confirmed in 100 of 3120 (3.2%) patients in CTC group and in 107 of 3163 (3.4%) in OC group (similar detection rates). 123 and 121 advanced neoplasms were found in CTC and OC groups, respectively. 14 cancers were found in CTC group and 4 cancers in OC group. The referral rate for OC in the primary CTC group was 7.9% (246 of 3120 patients). The total numbers of polyps removed in the CTC and OC groups were 561 and 2434, respectively.	Kim *et al*[45]
II. STOOL/FECAL-BASED TEST						
30.2% of patients were 50–59 years old; 39% of patients were 60–69 years old; 30.8% of patients were 70 or older	8104 study patients; 8065 were screened by Hemoccult II; 7904 were screened by Hemoccult II Sensa; 7493 were screened by HemeSelect; 7847 were screened by Hemoccult II Sensa and HemeSelect	Hemoccult II (detects the pseudoperoxidase activity of heme); Hemoccult II Sensa (detects the pseudoperoxidase activity of heme-more sensitive than Hemoccult II); HemeSelect (immunochemical test for human hemoglobin)	Once	No	The sensitivity for detecting carcinoma with Hemoccult II was 37.1% (95% CI: 19.7–54.6%), with combination Hemoccult II Sensa and HemeSelect was 65.6% (95% CI: 47.6–83.6%), with HemeSelect was 68.8% (95% CI: 51.1–86.4), and wotj Hemoccult II Sensa was 79.4% (95% CI: 64.3–94.5%). Specificity for detecting carcinoma was 86.7% with Hemoccult II Sensa, 94.4% with HemeSelect, 97.3% with combination test and 97.7% with Hemmoccult II .	Allison *et al.*[46]
50–74 years	15,011 patients	gFOBT-guaiac-based fecal occult blood test (arm 1); FIT-immunochemical FOBT(arm 2); FS – flexible igmoidoscopy(arm 3)	Once	Yes	gFOBT was positive in 2.8%, FIT in 4.8%, and FS in 10.2%. Detection rates for advanced neoplasia were: for FIT arm, 2.4%(OR 2.0 CI: 1.3–3.1); for FS arm, 8.0% (OR 7.0 CI: 4.6–10.7); for gFOBT arm, 1.1%. FS had a higher diagnostic yield of advanced neoplasia per 100 screened patients (2.4%) than gFOBT (0.6%) or FIT(1.5%).	Hol *et al.*[47]
50 years and older (mean 68.6 years)	4404 patients evaluated	Colonoscopy; Hemoccult II (detects the pseudoperoxidase activity of heme); the fecal DNA panel (21 mutations)	Once	648 patients were randomly selected for analysis from 1627 patients with minor polyps (tubular adenomas < 1 cm and hyperplastic polyps); 1423 patients were randomly selected for analysis from 2318 patients with no polyps	Colonoscopy detected invasive adenocarcinoma in 31 patients. The fecal DNA panel detected 16 of 31 cancers (sensitivity 51.6%). Hemoccult detected 4 of 31 cancers (sensitivity 12.9%) ($P = 0.003$). Among 418 patients with advanced neoplasia (cancers plus large polyps), the DNA panel was positive in 76 (18.2%) whereas Hemoccult II was positive in 45 (10.8%) ($P = 0.001$). As non-invasive test, the analysis of facal DNA detected a greater proportion of colorectal neoplasia than Hemoccult II test.	Imperiale *et al.*[48]

PREVENTION OF COLORECTAL CANCER

Prevention is defined as a medical activity that identifies significant various factors having important roles in carcinogenesis and that can be manipulated to alleviate their causal roles. Typically, prevention can be divided into two main categories: primary and secondary. Primary prevention of colorectal cancer includes a list of etiologic factors responsible for the development of this malignant disease. Among these are diet, energy intake, lifestyle and physical exercise, tobacco and alcohol use, parity, hormone use, and non-steroidal anti-inflammatory drug use. The list includes the prevalent factors regarding individuals with an average risk of colorectal cancer development. On the other hand, secondary prevention focuses on the identification of high-risk populations, embracing persons at increased risk of death from colorectal cancer in the presence of premalignant lesions or diagnosed early cancers. Secondary prevention strategies are used in, for example, the removal of adenomatous polyps by colonoscopic procedure, or even excision of the large bowel in familal adenomatous polyposis. Secondary prevention can therefore be used when a high-risk population of persons or patients has been characterized as needing accurate management to prevent colorectal cancer spreading. Table 8.2 presents factors important for primary and secondary prevention against colorectal cancer.

As indicated above, there are many factors of different categories that play important roles in colorectal carcinogenesis, and it is beyond the scope of this chapter to discuss them all. However, primary prevention of colorectal cancer by dietary modifications may be of critical value for all humans to be protected against colorectal cancer development, even if only partially. It seems that wheat, and especially wheat bran, consumption could be an important factor in providing health benefits in the sphere of colorectal cancer prevention.[49–51]

TABLE 8.2 Factors Important for Primary Prevention or Secondary Prevention of Colorectal Cancer

Primary Prevention	Secondary Prevention
Age ≥ 50	Family history of colorectal cancer or polyps
Diet with low fiber and high animal fat (increased risk)	Familial polyposis syndromes (Peutz-Jeghers syndrome, Gardner syndrome, juvenile polyposis)
Alcohol and tobacco use (increased risk)	Hereditary non-polyposis colon cancer (Lynch syndromes I & II)
Energy intact resulting in overweight and obesity (increased risk)	Inherited colorectal cancer in Ashkenazi Jews
Sedentary lifestyle with low physical activity (increased risk)	Medial control of infammatory bowel disease
Detection of inflammatory bowel disease and adenomatous polyps (jump in secondary prevention)	Bowel status after pelvic irradiation

WHEAT CULTIVATION, CROPPING, AND BIOLOGY

Wheat is a well-known cereal grain that is grown on arable lands and is responsible for sustaining commercial food production worldwide. Wheat is the most important source of vegetable protein in human food and has the highest protein content in comparison with other cereals such as maize or rice. Wheat appears to be the most widely grown crop in the world. It represents a renewable resource for food, animal feed, and various kinds of industrial processes involving food. Wheat grows widely in various areas, but the best climate is found between latitudes 30–60 N and 27–40°S. It can be cultivated at elevations ranging from sea level to 3000 meters. Soil for wheat cultivation should be neutral to slightly acidic (pH 5.5–6.5), and the temperature approximately 25°C. All wheat species are annual plants. The most popular are spring wheat plants, which are planted in the spring, have a short growing season (less than 100 days), and are harvested in the fall. Conversely, winter wheat grains are planted in the fall and harvested in early summer. The average farm yield for wheat is approximately 3 tonnes per hectare, and the most productive farms are in The Netherlands and Belgium, where the yield is 8.9 tonnes per hectare. Wheat is a major staple crop worldwide, with consumption running at approximately 30% of dry matter and 60% of the daily calorie intake in some developing countries.[52,53]

Wheat (*Triticum* spp.) together with barley (*Hordeum* spp.) form the Poaceae, the largest family within the monocotyledonous plants, which constitute the most important cereal crops in the world. The genetics of wheat species is more complicated than in most other domesticated plants because some are diploid while others are stable polyploids, tetraploid, or even hexaploid. Einkorn wheat (*Triticum monococcum*) is diploid (AA), with two complements of seven chromosomes ($n = 7$) ($2n = 14$). Tetraploid ($4n = 28$) species with four sets of chromosomes include emmer wheat (*Triticum dicoccum*), which is less important in modern agriculture, and durum wheat (*Triticum durum*), which is widely cultivated by farmers worldwide. Common wheat, also known as bread wheat (*Triticum aestivum*),

is a hexaploid species ($6n = 42$) that is widely used throughout the world. Spelt wheat (*Triticum spelta*), which is cultivated in limited quantities, is also considered to be a subspecies of common wheat.[54] The presence of certain versions of wheat grains depends on the genetic variation, which has a great impact in higher protein content, better cultivation, and crop yields. Wheat is used as human food or for animal feed. On the other hand, farro is a food product composed of various species of wheat. Genetic selection has an interesting history, starting back in antiquity during domestication.

THE HISTORY OF WHEAT DOMESTICATION

Cereals were the first species that were domesticated by man, at almost the same time as dogs, sheep, and cattle. This process has been discovered independently on all continents. In the case of practical plants, domestication appears as the suite of morphological and anatomical changes that follow cultivation necessary for an altered human environment. Thus domestication is different from conscious cultivation, which in fact began with related wild species. Evolutionary botany is a natural discipline that uses molecular genetics tools and draws knowledge from archeological investigations and that may more precisely reconstruct the evolutionary scenarios of wheat domestication. Why farming became a turning point for the evolutionary progress of humankind will probably never be known. Some ethnologists claim that demographic expansion was the main cause for humans becoming farmers, in order to increase food resources due to an increase in human population; and the practice of primitive agriculture required more energy than hunting and gathering, so agriculture became a necessity rather than an adaptation to novel inhabited environments.[55,56]

Salt and silt are two important factors in the development of Mesopotamian agriculture. The semiarid climate with low soil permeability is responsible for dangerous accumulations of salt, which is harmful to crops and soil texture. This process is responsible for the progressive changes that contributed to the settlement and development of past civilizations regarding necessary plant cultivation and animal husbandry.[57] Wheat is one of the first cereals that were domesticated from the wild species, characterized by its ability to self-pollinate, which greatly facilitated the selection of more practical species. Archeological investigations suggest that wheat appeared in the Fertile Crescent and the Nile Delta.[58] Recent results have shown that einkorn wheat was domesticated at Nevali Cori in southern Turkey 9000 years ago. Domestication is considered to have been a series of events, occurring at different places over many thousands of years, during which wheat persisted in cultivated fields. It has been suggested that domestication was a gradual process, being a result of the sedentary existence of our ancestors in the early villages of the Near East.[59] On the other hand, there have been results indicating that processing of wild cereal grains in the Upper Paleolithic (Ohalo II, Israel) was practiced at least 12,000 years before domestication in southwest Asia. The oldest evidence for processing of wild cereals as starch grains from barley and wheat was noted in grinding stones.[60]

One of the oldest mummies in the world, found in the Alps and better known by the popular humanizing nickname Ötzi, died at the age of 46 years approximately 5300 years ago. The corpse was perfectly preserved in ice for such a long time that meticulous investigations led to remarkable opportunities for extraordinary findings, including the contents of the colon, where the food residue had been preserved. Botanical assessment of the colon contents revealed bran and other remains of einkorn wheat and barley (45%), pollen (22%), and charcoal particles of coniferous wood (25%). Moreover, these studies revealed that Ötzi had been omnivorous, eating the meat of red deer and ibex.[61,62]

As indicated, domestication of plants and animals is the main factor responsible for changes in the development of human civilization. A pivotal position in the domestication of plants during early human agriculture development is held by einkorn wheat. For more than 50 years, the progress of molecular biology progress and its effective molecular techniques with appropriate scientific strategies have been playing a critical role in the determination of some wild species of plants that can be fully used as practical plants in modern agriculture. Phylogenetic analysis based on the allelic frequency of 288 amplified fragment length polymorphism marker loci, indicating a wild group of *Triticium monococcum boeticum* from the Karacadag mountains (southeast Turkey) that was likely the progenitor of cultivated einkorn wheat cereals. Moreover, archeological excavations of early agricultural settlements have supported this molecular conclusion.[63–65]

THE DEFINITION OF WHEAT BRAN AND DIETARY FIBER, AND A BRIEF CHEMISTRY

Industrialization and Westernization have led to the most prevalent ways of living in the modern world. Whether they always lead to a better and healthier life is highly debatable when taking into account new life-threats related to a disease associated with the progress

of our civilization. Nearly 70 years after World War II ended, everyday living has been changing with an increase in wealth of entire societies – at least, this is a main goal of democratic governments. However, we know that an energy-dense, low-fiber diet, which is especially popular in economically developed parts of the world, plays a major role in the development of many diseases, such as obesity, cardiovascular disease, type 2 diabetes, and cancer.

The problem of eating the indigestible parts of plants in the context of pregnancy toxemia was described for the first time in 1953 by Eben Hipsley.[66] In the 1970s, Burkitt and Trowell shed some light on fiber, defined more than 20 years earlier, regarding its beneficial effects on cardiovascular disease, type 2 diabetes, and cancer.[67] It appeared that the intake of dietary fiber should have a major role in sustaining health in the sphere of some diseases that appear frequently in society. It is necessary, then, to define the term "dietary fiber". Initially, fiber was defined as insoluble fibrous plant material that was not digested in the upper intestinal tract, but this definition has changed with accumulated knowledge on the chemistry of dietary fiber. Dietary fiber is presently defined as carbohydrates consumed as food, which cannot be fully digested or absorbed in the upper intestinal tract. Carbohydrates are polymers with 10 or more monomeric units, which are not hydrolyzed by endogenous enzymes in the small intestine and belong to one of the following groups: (1) edible carbohydrate polymers that occur naturally in food as consumed; (2) carbohydrate polymers that have been obtained from raw material in food by physical, enzymatic, or chemical means, and have been shown, by generally accepted scientific evidence by competent authorities, to have beneficial physiological effects on health; (3) synthetic carbohydrate polymers that have been shown, by generally accepted scientific evidence by competent authorities, to have beneficial physiological effects on health. Thus, fiber compounds can be either soluble or insoluble in water. Soluble compounds behave like colloids; they are viscous and form gels, have the capacity to hold water, and can bind to or be adsorbed by bile acids and other organic molecules.[68,69] Wheat is a well-accepted source of protein, carbohydrates, minerals, B group vitamins, and dietary fiber, and is therefore considered to be an excellent health-building food.[70] Dietary fiber is mainly composed of starch and polysaccharides that occur naturally in plants. Table 8.3[71,72] lists chemical compounds that are present in dietary fiber, along with a brief description. There is also a group of various substances that are often associated with fiber but do not qualify to be included within the definition of dietary fiber, such as phenols, waxes, cutin, phytic acid, and phytosterols.[72]

BIOLOGICAL ACTIVITY OF WHEAT BRAN AND DIETARY FIBER COMPOUNDS IN COLORECTAL NORMAL AND CANCER CELLS

Accumulated evidence indicates that dietary fiber consumption may have a role in the prevention of development of colorectal cancer, closely associated with direct effects on stool bulk and bile acid output.[73–75] A number of mechanisms are postulated to play roles, as a result of fiber consumption, in the prevention of colorectal cancer development, including intestinal transit time, adsorption of metabolically active materials, intraluminal antioxidant activity, the chemical environment of the colon, and fecal flora and bacterial enzymatic activity. Dietary fiber is resistant to human intestinal enzymes, which may explain the greater fecal bulk seen with higher fiber intake. This leads to lower colonic exposure to carcinogens through a simple dilution effect due to fiber consumption.[76,77]

A body of accumulating animal evidence has shown that wheat bran plays a critical role in the prevention of development of a range of cancers, especially colorectal and breast. Wheat bran is a rich source of dietary fiber that includes many structures and chemical substances enabling protective activity against carcinogens. Dietary fiber makes up less than half of wheat bran; the rest consists of phytochemicals such as phytic acid, and various phenolic components (phenolic acid, lignans, and flavonoids).[78] The effects of wheat bran consumption at the macro level are mainly associated with the reduction in transit time, increased fecal bulking, and the dilution of potentially carcinogenic compounds. Fermentation of wheat bran by colonic bacteria produces short-chain fatty acids, including acetate, propionate, and butyrate, which are rapidly absorbed by the colonic mucosa. Butyrate is the main source of energy for epithelial cells lining the colon, and has a range of effects relevant to reducing colorectal cancer risk.[79] Conversely, when protein is fermented in the colon for a longer time, by-products such as ammonia and phenols (*p*-cresol and phenol) may be harmful in facilitating carcinogenesis. Supplementation of wheat bran consumption, especially directed against ammonia and phenol products, could be achieved by the use of resistant starch (i.e., undigested carbohydrate present in the colon lumen) which has physiologic characteristics such as increasing concentrations of short-chain fatty acids, a lower pH, and lower levels of ammonia, phenols, and secondary bile acids.[80] Many mechanisms have been reported that could explain, to a greater or lesser degree, the preventive activity of wheat bran, and in fact of its two main parts – i.e., dietary fiber and wheat bran oil (lipid fraction of wheat bran). Wheat bran fiber supplementation can inhibit cell proliferation of stimulated normal colon mucosa or colorectal cancer cell lines; moreover, inhibition of DNA synthesis has been detected.[81,82]

TABLE 8.3 Chemical Compounds of Dietary Fiber with Short Characterization[71,72]

Larger Structure	Chemical Group	Chemical Compound	Structural Description And Characteristics
Resistant and slowly-digested starch stored in plants as crystalline granules	–	Amylopectin	70–80% of edible starch as large branched molecules of more than 10,000 glucose monomers
		Amylose	20–30% of edible starch as fewer glucose monomers linked by α 1:4 glycosidic linkages
Non-starch polysaccharides	Glucans (insoluble or soluble state)	β-glucans	Consist of approximately 250,000 glucose monomers in form of thermo-reversible, worm-like and cylindrical molecules; can be viscous or soft gel (weight dependent)
		Cellulose	Stiff structure, unbranched crystalline β-glucans consisting of 2000–15,000 glucose monomers
	Hemi-celluloses (insoluble or soluble state)	Arabinoxylans	Structure of twisted ribbon consisting of 1500–5000 L-arabinose branches
		Xyloglucans	Bind to surface of cellulose microfibrils; occur in cell walls; have glucose backbone with xylose side chains
		Glucomannan	Consists of chains of repeating units of glucose and mannose bound by β 1:4 linkages with short side chains
	Beta-fructans (only soluble)	Inulins	Linear fructans consisting of 20–1000 β 2:1 linked fructose molecules; enzymatic hydrolysis yields 3–-10 monomers
		Levans	Linear fructans made up of fructose molecules with β 2:1 and β 2:6 glycosidic links
		Graminans	Branched fructans consisting of β 2:1 and β 2:6 glycosidic-linked fructose molecules
	Galactans (only soluble)	Agar	Polymer of two classes of unbranched mixed α- and β-galactans: agarowe and agaropectin
		Corrageenans	Linear polymers of approximately 25,000 α-galactans
		Pectin	Complex, worm-like, flexible, acidic polysaccharides formed of partially methylated esters of α 1:4 D-galactose residues
	Mannans (only soluble)	–	Polymers of mannose complex structures
	Galacto-mannans (only soluble)	–	Consist of β 1:4 linked mannose backbone with α 1:6 D-galactose
	–	Xylan (only soluble)	Linear polysaccharide consisting of β 1:4 linked D-xylose (wood sugar)
Non-digestible oligosaccharides		Fructo-oligosaccharide	β 2:1 linear fructose polymer
		Galacto-oligosaccharide	Polymer of β-galactose molecules
		Raffinose-oligosaccharide	Trisaccharide consisting of galactose linked by α 1:6 linkage to sucrose
		Stachyose	Tetrasaccharide consisting of galactose and raffinose
		Verbascose	Pentasaccharide consisting of galactose and raffinose units

(Continued)

TABLE 8.3 Chemical Compounds of Dietary Fiber with Short Characterization[71,72]—cont'd

Larger Structure	Chemical Group	Chemical Compound	Structural Description And Characteristics
Sugar alcohols	Sorbitol, mannitol, erythriol, xylitol, isomalt, lactitol, maltitol	Erythriol	Absorber unchanged and oxidized partially to fructose
Non-digestible carbohydrate compounds bound to non-carbohydrate molecules	Glysocaminoglycan (bound to amino acids)	Chitin	Poly-glucosamino-glycan consisting of β-glucans linked by β 1:4 bonds to form acetyl-glucosamine
		Chitosan	Similar to chitin but less acetylated with lower molecular weight
		Hyaluronic acid (hyaluronian)	Non-sulfated polymer of glucoronic acid linked by glucosidic bonds to acetyl-glucosamine; viscous, slippery, and forms gel
	Glycoproteins (bound to proteins)	Psyllium	Combination of arabinoxylans, monosaccharides (arabinose, galactose, glucose, mannose, rhamnose, uronic acid, xylose); digested in upper intestinal tract, water-soluble, forms gels, holds water, binds organic molecules and is fermented in large bowel
		Gluten	Consists of gliaden, holdein, secalin, zein (avenin), and glutelin (protein) –;all proteins responsible for immune reaction in celiac disease
		Heparan sulfate	Consists of two or three glucosaminoglycan chains of acetyl-glucosamine linked to glucuronic acid and iduronic acid
		Dermatan sulfate	Made up of cross-linked glucosamino-glycans, chains of acetyl-galactosamine and D-glucoronic or iduronic acid
		Chondroitin sulfate	Composed of glycosamino-glycan chain of more than 100 alternating acetyl-galactosamine and β-D-glucuronic acid
		Keratan sulfate	Large, highly hydrated glycoprotein composed of glycosamino-glycan of repeating units of acetyl-galactosamine and galactose
	Saccharides (bound to terpens and phenols)	Saponins	Group of complex linear or branched hydrophilic glycosides (glucose, galactose, xylose, glucuronic acid); insoluble in water, bind bile salts and organic material in intestine tract, make foam in water
		Lignins	Insoluble in water, not fermented in colon, complex phenolic macromolecule covalently linked in cellulose microfibrils in cell walls, filling spaces between cells, which is responsible for mechanical strength of plants

The results of such a broad biological activity of wheat bran rely on both the inhibition of cell proliferation in the case of cancer cells, and the development of aberrant crypt foci dispersed in normal colon mucosa.[83–85] Wheat bran oil has also strong colonic tumor inhibitory properties. The main mechanism leading to anticancer activity is probably associated with the alteration of iNOS (inducible nitric oxide synthase) and COX (cyclooxygenase)-1 and -2 enzyme activities. The anticancer action of wheat bran oil has been demonstrated in the Apc(Min/+) mouse model.[86,87] A mixture of chemical compounds present in wheat bran and whole grains has multidirectional pharmacological activities that could be responsible for a reduced risk of chronic disease and cancer. One of the most important mechanisms readily seen in anticancer action is antioxidant activity. Among the most active compounds that have such anticancer activity are phenols (ferulic acid) and other bound phytochemicals.[88]

Psyllium

Psyllium (ispaghula) is the common name for several plants belonging to the genus Plantago and whose seeds are primary used for the production of mucilage. Dietary fiber contains psyllium, which is a glycoprotein that is not absorbed by the small intestine. Structurally, psyllium is a complex chemical compound (see Table 8.3), being a soluble fiber with a mechanical action associated with its mucilaginous nature and reliance on the absorption of excess water while stimulating normal bowel elimination. Psyllium has both positive and negative effects; on the positive side, it is linked to normalization of higher levels of plasma cholesterol.[89]

Some experimental results have also shown that psyllium along with wheat bran can enhance inhibition of colon cancer, giving greater protective effects against azoxymethane-induced colonic tumors in Fischer-344 rats. Psyllium and wheat bran are active partners in maximum mammary tumor-inhibiting effects through decreased cecal β-D-glucuronidase activity due to the increased psyllium content. Unfortunately, no statistical significant differences in circulating estrogens or urinary estrogen excretion were observed.[90,91]

On the negative side, ingestion of a psyllium-containing cereal can lead to anaphylaxis that may end in death in sporadic cases.[92]

Fermented Wheat Germ Extract (FWGE, Avemar, Awge)

FWGE is defined as an extract of wheat germ derived from the germ of a wheat plant. It is available commercially as a dietary supplement, being the product of industrial fermentation of wheat germ and having a unique characteristic that is useful in anticancer management. Avemar pulvis is a powder consisting of an aqueous extract of fermented wheat germ with maltodextrin and silicon dioxide, standardized to contain circa 200 μg/g of the natural constituent 2,6-dimethoxy-p-benzoquinone.[93,94]

The chemical composition of FWGE is complex because it is a multisubstance compound with two main biologically active entities: 2-methoxy benzoquinone and 2,6-dimethoxy benzoquinone. Biochemically, FWGE interferes with anaerobic glycolysis, the pentose cycle, and ribonucleotide reductase. Four mechanisms of action are postulated: a metabolic effect, an antiproliferative effect, an antimetastatic effect, and an immunological effect.

1. The metabolic effect of FWGE relies on inhibition of glucose uptake in cancer cells and interference with enzymes of anaerobic glycolysis – transkelotase, glucose-6-phosphate dehydrogenase, lactate dehydrogenase, and hexokinase. All the enzymes are necessary for the allocation of precursors for RNA and DNA synthesis.
2. An antiproliferative effect has been investigated in human tumor models *in vitro* and *in vivo*. Such experimental studies have shown potential antitumor activity in colon, testis, thyroid, ovary, lung, breast, gastric, head and neck, liver, glioblastoma, melanoma, cervical, and neuroblastoma human cancer cell lines. FWGE was found to reduce tumor growth in a dose-dependent manner.[95,96]
3. An antimetastatic effect has been observed alone or in combination with cytostatic drugs such as 5-fluorouracil or dacarbazine. Researchers used various tumor models, among them colon cancer cell lines, to demonstrate an antimetastatic effect of FWGE.[95,96]
4. An immunological effect was observed in preclinical studies when FWGE's action could not be attributed to its direct antiproliferative effect. *In vivo* experimental models have shown that FWGE is also effective by enhancing the activity of the immune system, for example, by stimulating NK cells (by reducing MHC I molecule expression), enhancing TNF secretion by macrophages, or increasing ICAM1 molecule expression on the vascular endothelial cells.[95,96]

FWGE appears to have an impact in reducing colon carcinogenesis induced by azoxymethane, as used in Fischer-344 rats. The antitumor activity of FWGE is mainly associated with previously described postulated mechanisms. A relatively new path that needs meticulous investigation is the inclusion of FWGE in combination with other well-accepted anticancer drugs, such as 5-fluorouracil, oxaliplatin or irinotecan,

that have been clinically tested in the treatment of colorectal cancer patients. The most biologically active part of FWGE is benzoquinone, which itself has not been toxic in tested doses, but has anticarcinogenic action.[97–99] Aleurone is a protein that occurs in the form of minute granules, or in a special peripheral layer, in the endosperm of seeds. Fermentation of dietary fiber by microflora enhances the levels of effective metabolites to protect normal colon epithelium against malignant transformation. Wheat aleurone is a source of dietary fiber and has many biological activities, including regulation of cell growth, apoptosis, and differentiation. These processes could be responsible for the cancer-preventive action of fermented wheat aleurone in the colon.[100,101]

FWGE has mainly been tested in experimental models, but clinical trials have also been performed in patients with colon cancer and melanoma. In melanoma, a randomized pilot Phase II study was carried out in an adjuvant setting with the use of FWGE.[102] The open-label cohort trial was designed to compare anticancer treatments plus FWGE (dose of 9 g daily through 6 months) with anticancer treatments alone in colorectal cancer. The experimental group comprised 66 colorectal cancer patients, and the control group 104 colorectal cancer patients. End-point analysis revealed that progression-related events were significantly less frequent in the experimental group with FWGE treatment than in controls: new recurrences 3% vs 17.3%, $P < 0.01$; new metastases 7.6% vs 23.1%, $P < 0.01$; deaths 12.1% vs 31.7%, $P < 0.01$, respectively. Survival analysis showed significant improvements in progression-free survival ($P = 0.018$) and overall survival ($P = 0.027$) in patients given FWGE.[103]

Lignans

Lignans are chemical compounds, defined as phytoestrogens, found in plants. Plant lignans are polyphenols derived from phenylanaline (pinoresinol, lericiresinol, secoisolariciresinol, syringaresinol, or sesamin), and can be metabolized by intestinal bacteria to form mammalian lignans such as enerodiol and enterolactone. Lignans act as antioxidants and can bind to estrogen receptors in the breast tissue. The crucial role in the synthesis of mammalian lignins via the phenylpropanoid pathway is played by pinoresinol lariciresinol reductase.[104,105] Lignans (entroldiol and enterolactone) are involved in cytostatic activity against colon cancer cell lines. In spite of the lack of cytotoxicity, measured by proliferation capacity, DNA flow cytometry analysis revealed cell cycle arrest at the S phase with a readily seen decrease of cyclin A detected by Western blotting.[106]

Lignins

Lignins originating from wheat cereal may be responsible for protective activity against cancer.[107,108] Lignins are complex chemical compounds that fill the spaces in the cell walls between cellulose, hemicellulose, and xylem, forming tracheids and vessels in higher plants. Although lignins are indigestible by animal enzymes, they can be precursors of mammalian lignans.[109,110]

Tricin

Tricin is a flavonoid that was primarily found in rice bran, but can also be found in other grass species such as wheat, barley, and maize. Tricin can be prepared by chemical synthesis via the Baker–Venkata–Raman reaction between acetylsyringic acid and phloroacetophenone, or by separation by high performance liquid chromatography from an antioxidant product derived from bamboo leaves.[111] Tricin exhibits antigrowth activity in several human cancer cell lines via its well-expressed anti-inflammatory potential. Experimental results collected after determining tricin inhibitory activity against inflammation-related colon carcinogenesis in male Crj:CD-1 mice relied on decreased expression of TNF-α in the non-lesional crypts in the colon mucosa and the proliferation of adenocarcinomas.[112]

Phytic Acid

Phytic acid is a major fiber-associated component of wheat bran and legumes. The principal role of phytate in many plants is storage of phosphorus, especially in bran and seeds. Phytic acid, also known as hexaphosphorylated inositol (IP6), can be internalized by cells, and can therefore be responsible for changes in the biochemical functions of secondary messengers. Phytic acid targets cancer cells by modulation of cell signaling, alterations in the cell cycle, non-homologous end-joining DNA repair, or activation apoptosis.[113,114] Dietary fiber with endogenous phytic acid component, and pure exogenous phytic acid added to a low-fiber diet, can increase the rate of apoptosis and degree of differentiation in the distal colon.[115] One of the significant molecular targets for phytic acid appears to be nuclear factor-κB (NF-κB), a well-known member of the transcriptional factor family, which plays important roles in regulating the expression of genes involved in a number of cellular processes. Results of an experimental study performed on the colon cancer cell line Caco-2 showed that phytic acid primarily influences p65 (the NF-κB subunit) and IκBα gene expression by their stimulation, which is responsible for inhibition of cancer cell proliferation.[116]

Lunasin

Lunasin is a 43-amino acid peptide derived from the soybean 25 albumin seed protein that has both anticancer and anti-inflammatory activities. Although initially isolated in soybean, lunasin has recently also been isolated in barley and wheat. More recent experimental studies have demonstrated that lunasin can inhibit the growth of some cancer cells both in culture and in mouse *in vivo* models.[117–119] Lunasin is a unique peptide that contains, at its carboxyl end, nine asparagine residues, the RGD (arginine–glycin–asparagine) cell adhesion motif, and a predicted helix with structural homology to a conserved region of chromatin-binding proteins. The molecular and functional structure of lunasin has been confirmed in experiments showing arrest of mitosis, leading to apoptosis, when mammalian cells were transfected with the lunasin gene. This peptide binds to deacetylated histones and inhibits their acetylation. Therefore, when histones H3 and H4 are deacetylated, activities of histone acetyltransferase and phosphorylation of the Rb protein cannot be performed. The chemopreventative action of lunasin therefore seems to be a highly regulated acetylation-dependent process.[120,121] Lunasin has caused cytotoxicity to colon cancer cell lines and induced G2/M cell cycle arrest with a simultaneous increase in p21 expression. Apoptosis induced by lunasin has been stimulated by increased activity of caspase-9 and caspase-3. Effective cytotoxicity of lunasin against colon cancer cell lines has additionally been correlated with the expression of $\alpha_5\beta_1$ integrin.[122,123] Chemotherapeutics, especially oxaliplatin, play a pivotal role in colorectal cancer management. *In vitro* experimental results have demonstrated that lunasin potentiates the effect of oxaliplatin in preventing metastasis formation, by an $\alpha_5\beta_1$ integrin-dependent mechanism that suppresses FAK/ERK/NF-κB signaling.[124]

Apigenin

Apigenin is a natural flavone found in many plants. Natural flavones such as apigenin, naringenin, luteolin, tangeritin, and baicalein have many biological functions. Apigenin is abundantly present in common fruits and vegetables, including parsley, onions, oranges, tea, chamomile, and wheat sprouts, among others. It has been shown to possess significant anti-inflammatory, antioxidant, and anticarcinogenic properties.[125] In the carcinogenesis of colorectal tumors, it is accepted that aberrant crypts can be demonstrated (although not in all cases) and that this process depends mainly on the biological nature of the colon cancer. A diet containing apigenin was experimentally demonstrated to reduce by 57% ($P<0.05$) more than four aberrant crypts/focus in azoxymethane-treated Sprague-Dawley rats. On the other hand, naringenin lowered both the number of crypt foci by 51% ($P<0.05$) and the proliferative index by 32% ($P<0.05$). Both apigenin and naringenin increased apoptosis of luminal colon mucosa cells (78% and 97%, respectively; $P<0.05$).[126] Apigenin along with TRAIL (human tumor necrosis factor-related apoptosis-inducing ligand) is responsible for induction of apoptosis by increased interaction of bcl-2 with caspase-8, -10, -9, and –3. These molecular events were detected only in colon cancer cell cells and other human cancer cell lines, and not in normal human peripheral blood mononuclear cells.[127] Various molecular mechanisms of the anticancer activity of apigenin have been reported. Both *in vitro* and *in vivo* studies have demonstrated that apigenin suppresses the growth of colorectal cancer cells via phosphorylation and upregulated expression of FADD (Fas-associated protein with death domain), and induction of proapoptotic proteins (NAG-1, p53) and the cell cycle inhibitor p21.[128,129] Metastasis formation in cancer progression is a turning point in the whole course of malignant disease. Therefore, there is a great need to find means of hampering or blocking metastasis formation. It seems that apigenin has a mechanism that could inhibit metastasis formation by CD26 molecule functions. CD26 is a multifunctional cell-surface protein that, through its associated dipeptidyl peptidase (DPPIV) and ectoadenosine deaminase (eADA) enzyme activities, can suppress pathways involved in tumor metastasis formation. Apigenin clearly upregulated cell-surface CD26 on human colorectal cancer cells (HT-29, HRT-18).[130]

Summary

Chemical compounds present in wheat bran are characterized by multifunctional activities, especially when assessed at the cellular and molecular levels. Some of the described substances are worth investigating in the context of supplementary helpers used during the arduous process of colorectal cancer treatment. The use of wheat bran-originating compounds along with anticancer drugs given alone or together with monoclonal antibodies, or with radiotherapy, which is especially important in patients with rectal cancer, appears to offer abundant future work for both laboratory scientists and physicians.

WHEAT BRAN CONSUMPTION, ADENOMATOUS POLYPS, AND COLORECTAL CANCER

The Irish surgeon and physician Dennis Burkitt is well known for his medical missionary work in Africa. In 1957, he and his co-workers identified the lymphoma that bears his name. His next success was firmly

associated with observing disease patterns, and led to the nickname "fibreman". While working in Africa, Burkitt claimed that he had seen hardly any cases of many of the most common diseases in the United States and England. He hypothesized that these Western disorders had a single causative factor: deficiency of dietary fiber.[131] The medical problem of deficiency of dietary fiber is reflected throughout many fields of modern medicine, ranging from metabolic diseases and cardiac illnesses to cancer.[132]

Dennis Burkitt, as an astute clinician, drew his conclusions from meticulous surveys, but he did not have any knowledge of the biochemical and molecular background that represents dietary fiber/wheat bran deficiency in everyday eating. Food and feed represent an exceptional example of fast-growing market in which dietary supplements appear to have a critical role either in economic development by increasing profits, or in promotion of health. Therefore, it is necessary to have hard data regarding the role of many supplementary factors such as vitamins, minerals, and dietary fibers, reflecting the status of health among consumers. A variety of food chemical compounds used as ingredients of bread, whole grain cereals, and other snacks is frequently eaten by modern humans. Therefore, it is easy to hypothesize that food appears to be an important factor responsible for sustaining health, reflected by the longer lifespan among humans living in modern societies. Food has therefore probably had an exceptional role in the prevention of many diseases that naturally occurred in the past.[133–135]

The well-accepted fact that only 5–10% of all cancer cases are due to genetic defects leads to the conclusion that the remaining 90–95% are due to lifestyle factors such as diet, smoking, alcohol, physical activity, obesity, and sun exposure. The EPIC (European Prospective Investigation into Cancer and Nutrition) study was specifically designed to investigate the relationship between diet and cancer and other chronic diseases. The results showed the following associations in the gastrointestinal tract:

> Gastric cancer was inversely associated with high plasma vitamin C, some carotenoids, retinol, α-tocopherol, a high intake of cereal fiber, and high adherence to the Mediterranean diet, while red and processed meats were associated with increased risk. A high intake of dietary fiber, fish, calcium, and plasma vitamin D was associated with a decreased risk of colorectal cancer, while red and processed meat intake, alcohol intake, high body mass index (BMI), and abdominal obesity were associated with increased risk.[136]

Most of the present studies can be grouped as observational studies or intervention studies. Well-known limitations of observational studies embrace the collection and interpretation of dietary data, and therefore constrain conclusions from these studies. However, intervention studies testing the relationship between dietary fiber and colon cancer have focused on whether fiber supplementation or diet modification can affect the risk of adenomatous polyps, or even colorectal cancer, appearing. The blurred status of collected data evident at the interpretation stage, where final conclusions are hampered mainly by differences in dietary measurements, lack of standardization of supplemental sources, differences in metabolism among individual participants of the studies, and the retrospective nature of older studies. How these studies are designed and then performed is crucial to the level of evidence: level I evidence is derived from randomized, double-blind controlled clinical trials; level II evidence originates from well-designed controlled clinical trials or well-designed multicenter, prospective cohort, or case–control epidemiologic studies; and level III evidence comes from respected authorities with clinical experience, descriptive studies, or other clinical reports.[137–139]

Colorectal adenomatous polyps are defined as precursors to colorectal cancer. The relationship between diet and the appearance of polyps should help in identifying modifiable factors, with the paramount goal of decreasing the risk of colorectal cancer and reducing its incidence and mortality. It is accepted that adenomatous polyps are an informative endpoint for colorectal carcinogenesis. Several case–control studies[140–149] have shown inverse associations between fiber and colorectal adenoma. On the other hand, intervention studies have shown no protective association of a high-fiber diet or supplementary use of dietary fibers.[150–154]

In a randomized, partially double-blinded, placebo-controlled factorial trial, MacLennan *et al.*[155] showed that a modified diet with fat reduced to 25% of the total calories and daily supplementation with 25 g of wheat bran and a 20-mg capsule of β-carotene did not act preventively by significantly lowering the rate of new adenomas, but did reduce the risk of large adenomas (≥ 10 mm), although not in a statistically significant way. The American PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial was defined as a randomized controlled trial designed to investigate early detection of colon cancer and adenomas. Participants in the highest quintile of dietary fiber intake had a 27% (95% CI: 14–38, $P_{trend} = 0.002$) lower risk of adenoma than those in the lowest quintile. The range of total dietary fiber intake in the study population for the 10th to 90th percentiles was 12.6–36.4 g/day.[156] Despite the fact that evidence for an association between dietary fiber intake and colorectal polyps and cancer has been equivocal, there are some data showing a difference in response to fiber consumption between sexes. Results of the Wheat Bran

Trial and the Polyp Prevention Trial have shown that the adjusted odds ratio for adenoma recurrence in the intervention group was 0.91 (95% CI: 0.78–1.06), but for men the intervention was associated with statistically significant reduced odds of recurrence (0.81; 95% CI: 0.67–0.98) while for women no significant association was observed.[157] Diet modifications have also been assessed in interventional studies: in some studies dietary adherence to a low-fat, high-fiber diet was associated with a reduced risk of adenoma recurrence at the level of 35%, but in others no such result was found.[158,159]

Discrepancies in collected evidence are probably dependent on many other factors that have not been properly monitored or are even unknown, such as vitamins; active chemical compounds working co-carcinogenically or anti-carcinogenically and appearing during colonic fermentation; minerals – for instance, selenium, which has an inverse association with a decreased risk of colorectal cancer;[160] or other factors such as the inflammatory response in direct relation to functions of interleukins such as IL-1β, IL-8, IL-10, and IL-6.[161,162] The latter is considered to be a potential indicator for prevention of high-risk adenoma recurrence.

The link between dietary fiber intake and prevention of colorectal cancer was suggested more than 40 years ago. Clinical trials focusing on the role of wheat bran fiber supplementation in lower colorectal cancer risk have largely been performed safely, without significant gastrointestinal side effects and changes in body weight.[163] Many clinical trials establishing the association of dietary fiber intake with the risk of colorectal cancer have been performed, both as observational and as intervention studies. The results are conflicting, and it is impossible to draw final conclusions. A combination analysis of 13 case–control studies[164] and a meta-analysis of 16 case–control studies[165] presented an inverse association between fiber intake and risk of colorectal cancer incidence. In contrast to the above statement, 10 prospective studies avoiding the potential for recall and control selection bias have failed to support the association between beneficial dietary fiber intake and reduced risk of colorectal cancer.[166–175] However, the latest results seem predominantly to show a clinical benefit, by reduction of colorectal cancer risk, of consuming a 10-g daily dose of dietary fiber. Table 8.4[176–183] shows the results of clinical trials published since the year 2000.

Unfortunately, investigations regarding the relationship between wheat bran or dietary fiber intake and the reduced risk of colorectal cancer are not complete. There are many other problems, as indicated by the need to establish how dietary fiber should be mixed with other nutritional compounds. Which of the known sources of dietary fiber should be considered the best, taking into account the most frequently expressed beneficial results, indicating the clearest reduction in colorectal cancer risk? There is a question over the subject of how to maximize results by combining wheat bran or other sources of dietary fiber with NSAIDs (non-steroidal anti-inflammatory drugs), especially in patients with a propensity for colorectal polyps, or in the population of humans taking statins. Early results are encouraging, showing a reduced risk of colorectal cancer with 6-month interventions with atrovastin, sulindac, or ORAFTI® Synergy1 (a prebiotic fiber composed of oligofructose and polyfructose chains).[184]

Despite the real progress in medical management of colorectal cancer, it is still a huge challenge to achieve better results, because this malignant disease continues to constitute a significant proportion of the global burden of cancer morbidity and mortality. One million new cases of colorectal cancer are diagnosed each year and more than half a million people die from this disease – equivalent to approximately 8% of all cancer-related deaths worldwide.[185] More broadly defined needs for better results of preventive interventions must be supported by changes in lifestyle. This includes modification of the Western diet by increasing the consumption of plant foods and reducing red meat intake, along with maintenance of physical activity and appropriate body mass. Together, these activities should substantially reduce colorectal incidence and mortality.[186–188]

CONCLUSION

Colorectal cancer is still regarded as one of the most significant neoplasms, with a large number of cases diagnosed every year in industrialized societies. This form of cancer is responsible for a high rate of deaths among patients suffering from malignant disease. Many medical disciplines have made huge progress in the management of colorectal cancer: in diagnosis, gastroenterology offers modern techniques of visualizing the colonic mucosa and pathology gives a more precise diagnosis not only by assessment of cell morphology but by better molecular characterization; in surgery, modern surgical removal appears to be less invasive and patients recover faster than previously; and in oncology, chemotherapy has well-accepted significance either in the treatment of early colorectal cancer in an adjuvant setting, or in the advanced phase of the colorectal cancer in a palliative setting.

When knowledge shows clear causative relations among various factors, especially in cancers having tremendous importance in a society, it becomes necessary to use more active methods to change the action of harmful factors and hamper carcinogenesis. Colorectal cancer is considered to be one such important neoplasm, with a large number of cases worldwide, and an association with the Western lifestyle. It is a strong hope that both food and feed have important roles in tackling colorectal carcinogenesis. Accumulated evidence has shown

TABLE 8.4 The New Millennium Results of Clinical Trials on Dietary Consumption in Relation to Colorectal Cancer Risk

Study Design and Year of Report	Participants	Outcomes	Conclusions	References
Case–control (2001)	286 (174 males, 112 females) patients with histologically confirmed colon or rectal cancer vs 550 controls	OR: 0.55 for soluble non-cellulose polysaccharides; OR: 0.57 for total fibers; OR 58 for total insoluble fibers; OR 0.60 for vegetables; OR: 0.78 for fruit; OR: 0.74 for grain fibers	Significant inverse relationship of total dietary fiber intake with risk of colorectal cancer	Levi *et al.*[176]
Observational study – EPIC study (2003)	519,978	Adjusted RR: 0.75 (95% CI: 0.59–0.95) for highest vs lowest quintile of fiber intake; better protection for left side colon and for rectum Adjusted RR: 0.58 (0.41–0.85) highest vs lowest quintile of doubling fiber intake	Dietary fiber intake could reduce risk of colorectal cancer by 40%	Bingham *et al.*[177]
Prospective cohorts (2005)	76,947 women, 47,279 men	HR: 0.91 (95% CI: 0.87–0.95) for 5 g daily increase in fiber intake Adjusting for covariates used in EPIC study, HR: 0.99 (0.95–1.04)	Dietary fiber intake does not indicate important association with reduced colorectal cancer risk	Michels *et al.*[178]
13 Prospective cohort studies (2005)	725,628	Age adjusted RR: 0.84 (95% CI: 0.77–0.92)	Dietary fiber intake is inversely associated with risk of colorectal cancer in age-adjusted analysis; other dietary factors have no significant relationship	Park *et al.*[179]
Prospective nested case–control study (2010)	579 patients with histologically confirmed colorectal cancer vs 1996 controls	Multivariable-adjusted for colorectal cancer for highest vs. lowest quintile of fiber intake, OR: 0.66 (95% CI: 0.45–0.96, P_{trend} <0.012]	Dietary fiber intake is inversely associated with colorectal cancer risk	Dahm *et al.*[180]
Community-based case–control study (2010)	816 patients with histologically confirmed colorectal cancer vs 815 community controls	Soluble and insoluble dietary fibers are not associated with overall risk or subsite-specific risk of colorectal cancer	No protective association between dietary fiber intake and colorectal cancer risk	Uchida *et al.*[181]
25 prospective cohort and nested case–control studies (2011)	1.9 million participants in dietary fiber analysis and 14,400 cases of colorectal cancer	For 10 g daily of total dietary fiber (16 studies) RR: 0.90 (95% CI: 0.86–0.94, I^2 = 0%); for fruit fiber (9 studies) RR: 0.93 (0.82–1.05, I^2 = 23%); for vegetable fiber (9 studies) RR: 0.98 (0.91–1.06, I^2 = 0%); for legume fiber (4 studies) RR: 0.62 (0.27–1.42, I^2 = 58%); for cereal fiber (8 studies) RR: 0.90 (0.83–0.97, I^2 = 0%)	High intake of dietary fiber (cereal fiber) and whole grain are associated with reduced risk of colorectal cancer	Aune *et al.*[182]
Prospective Scandinavian HELGA cohort (2012)	108,081 cohort members with 1168 colorectal cancer patients (691 colon cancer and 477 rectal cancer)	For 10 g daily of total dietary fiber, IRR: 0.74 (95% CI: 0.64–0.86); for 2 g daily of total dietary fiber, IRR: 0.94 (0.91–0.98)	Dietary fiber has protective role against colon cancer but not rectal cancer	Hansen *et al.*[183]

Abbreviations: OR, odds ratio; RR, relative risk; IRR, incidence relative risk; HR, hazard ratio; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HELGA, Nordic Health – Whole Grain Food Project 070015.

heterogeneous results, with a slight bias in favor of a beneficial role of wheat bran/dietary fiber intake in the reduction of colorectal cancer risk. There is still the need, though, for more precise interpretation from planned controlled studies, showing how food consumption could modify the causative factors responsible for the pathogenesis of colorectal cancer. Therefore, a preventive action of food could offer more than even the most sophisticated methods of treatment of colorectal cancer, used at the disseminated phase of this malignant disease.

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WHEAT AND RICE IN DISEASE PREVENTION AND HEALTH

BENEFITS, RISKS AND MECHANISMS OF WHOLE GRAINS IN HEALTH PROMOTION

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