Dietary supplement use and colorectal tumors

From prevention to diagnosis

Renate C. Heine-Bröring

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ABSTRACT

Background

Expert guidelines formulated by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) advised no use of dietary supplements for cancer prevention. However, it is unclear whether those recommendations also apply to populations at high risk for incident or recurrent colorectal tumors specifically, since dietary supplement use is ubiquitous in western countries where colorectal tumors are common. Furthermore, before the association between dietary supplement use and recurrence and survival in colorectal cancer patients can be examined, more information about the consistency of dietary supplement use is needed, as it is plausible that use varies over time after colorectal cancer diagnosis. This thesis focuses on the association between dietary supplement use and colorectal tumor risk and recurrence in the general population and in high-risk populations, and describes the consistency of use in patients who were diagnosed with colorectal cancer.

Methods and results

First, we conducted a systematic literature review with meta-analyses of observational studies about the association between dietary supplement use and colorectal cancer risk. Our findings suggested inverse associations between multivitamins (use versus no use: RR=0.92; 95% CI 0.87–0.97, calcium supplements (use versus no use: RR=0.86; 95% CI 0.79–0.95) and colorectal cancer risk, while the association for other supplements and colorectal cancer risk was inconsistent.

Second, we investigated the role of dietary supplement use in recurrence of colorectal adenomas and advanced colorectal adenomas in a prospective cohort study of 565 patients with a history of sporadic colorectal adenomas. Dietary supplement use was not associated with total adenoma recurrence (HR=1.03; 95% CI 0.79–1.34).

Third, dietary supplement use and colorectal adenoma risk was examined in a prospective cohort study among 470 individuals with Lynch syndrome. No associations were found between dietary supplement use (HR=1.18; 95% CI 0.80–1.73) and colorectal adenoma risk in these individuals.

Finally, in an ongoing prospective cohort study among incident colorectal cancer patients we evaluated whether dietary supplement use was consistent over time. Dietary supplement use was extensively assessed with a detailed self-administered questionnaire at diagnosis, six months and two years post-diagnosis. We observed that dietary supplement use among

160 colorectal cancer patients was common at all time points, but use was inconsistent from diagnosis to two years post-diagnosis.

Conclusion

The results in this thesis do not point toward a preventive nor a harmful role for dietary supplement use in colorectal tumor risk and recurrence in the general population and in high-risk populations for colorectal cancer. However, dietary supplement use appeared to be inconsistent over time after colorectal cancer diagnosis, and use should be repetitively assessed over time. Since dietary supplement use is rising in countries where colorectal tumors are prevalent and the incidence of colorectal tumors will increase due to screening practices, research on the role of dietary supplement use for primary or tertiary prevention of colorectal tumors should continue in which use should be repetitively and comprehensively assessed.

For Arnoud & Carmen

Contents

Chapter 1

General introduction

BACKGROUND

Nowadays, a wide range of dietary supplements is commercially available, and media attention for supplements to prevent or treat health conditions is booming. Many individuals show considerable interest in self-acquired information on dietary supplement use via family, friends, books, or the internet. Consumers have access to an enormous selection and a diverse variety of dietary supplements, including single-ingredient products and various combinations of vitamins, minerals, botanicals, and other constituents. As a consequence, dietary supplement use has exploded over the past decades. [1,2] In the United States, more than half of the population currently uses dietary supplements, whereas use varies from country to country in Europe. [1,3] In European countries, a clear north–south gradient in dietary supplement use is present, with a higher consumption in northern countries: use ranges from 2% and 7% in Greece and Italy to 30%, 50%, and 65% in Sweden, the Netherlands and Denmark respectively. [1,3] In the United States and in Europe, supplement use appears to be higher among women, [2] among higher educated people, [2,4] and among people with a healthier diet and lifestyle. [4]

Although commercially available supplements are considered to be non-toxic, some supplements often contain 100 percent or more of the daily recommended intake of one or more nutrients thereby exceeding the tolerable upper intake levels as established by the European Food and Safety Authority (EFSA). [5] A daily intake of these products during longer periods cannot exclude a possible occurrence of detrimental effects on health and wellbeing. [6,7] Therefore, the Dutch expression 'Baadt het niet, dan schaadt het niet', i.e. 'if supplements do not have any health effects, they may also not be harmful', may not always apply. Nevertheless, many individuals believe that taking dietary supplements may be beneficial in the treatment of acute or chronic illnesses or for the prevention or recurrence of a serious disease, [8-14] and use may be perceived as a way to regain some control over their own health, illness, or treatment. [15] Until more evidence about the beneficial or harmful effects of dietary supplement use on overall health and chronic diseases, including cancer, is available, the high prevalence of use, the accessibility of supplements with a high nutrient content, and the risk of multiple and long-term supplement use are an area of concern.

The World Cancer Research Fund, and the American Institute for Cancer Research (WCRF/AICR) developed guidelines for food, nutrition, physical activity and prevention of cancer based on systematic literature reviews and meta-analyses. [16,17] For dietary supplement use in particular, the WCRF/AICR advises against the use of supplements

for cancer prevention, and recommends to meet nutritional needs through diet alone. [16] However, this recommendation is mainly based on randomized controlled trials reporting that dietary supplement use may also exert unexpected and uncommon adverse effects among those at relatively high risk of cancer, such as long-term smokers and men with a high risk of prostate cancer. [18] Those trials focused on the effect of use of specific dietary supplements and risk of tumors in the lungs and in the prostate showing convincing evidence for use of high-dose beta-carotene supplementation and an increased risk of lung cancer in smokers. [19-22] These results may, for example, be explained by acceleration of the growth of early lung tumors by antioxidants. [23] Inconsistent associations were found for use of vitamin E supplements and risk of prostate cancer. [19,24,25] Furthermore, a probable protective effect for high-dose supplemental selenium and prostate cancer risk was found, [26-29] but use of selenium supplements could probably increase the risk of type 2 diabetes mellitus. [30-34] Explanations for those findings could be the regulatory function through involvement of selenoproteins in testosterone production in both normal and abnormal prostate growth, [26,28] and new roles of selenoproteins in cellular energy metabolism, which may possibly lead to the increased risk of type 2 diabetes mellitus. [30]

However, it is not yet clear whether this recommendation for dietary supplement use also applies to individuals at high risk of colorectal tumors, i.e. those with previous colorectal adenomas or an inherited type of colorectal cancer, or to individuals with established colorectal cancer as the randomized controlled trials were conducted with the aim to study primary outcomes other than colorectal tumors. According to those trials with colorectal tumors as secondary outcomes, there is generally consistent evidence that use of calcium supplements protects against colorectal adenomas [35-39] and carcinomas [40-46] by its widely known inhibitory effects on colorectal carcinogenesis. [47] For supplemental folic acid [48-51] or antioxidants, [52] no clear decrease or increase in risk of colorectal adenomas or carcinomas was observed in meta-analyses of randomized controlled trials. However, very specific subgroups, such as postmenopausal women, [53,54] heavy smokers, [19,55] health professionals [21,56,57] and populations at high risk for cancer, [57-59] osteoporosis, [51] and cardiovascular diseases [60,61] were studied which makes it difficult to generalize the results and to relate the findings to widespread use among the general population. Another issue in trials is that participants take fixed and prescribed dietary supplements in specific settings and specific dosages, which might not necessarily be beneficial. For individuals with established colorectal cancer specifically, use of dietary supplements could be higher after diagnosis and may fluctuate during and after cancer therapy as those individuals believe that supplements

may improve their prognosis, overall health, and quality of life. [8-11,62,63] Nevertheless, it is yet unclear whether use of dietary supplements after colorectal cancer diagnosis might be beneficial or harmful as those supplements might interact with conventional cancer therapies. [7,64-67] Therefore, it is of great importance to get more insight into the role of dietary supplement use in colorectal tumor development in the general population and in high-risk populations for colorectal cancer as dietary and lifestyle factors, and thereby also dietary supplement use, are mostly associated with colorectal tumors in contrast to other types of cancer. [68,69]

Dietary supplement use and colorectal tumor risk in the general population

Dietary supplement use is ubiquitous in western countries where colorectal tumors are common. The prevalence of sporadic colorectal adenomas in the general population, which are benign precursors for colorectal cancer, [70-74] is around 20% in individuals aged 50 years, [75] and is increasing to 50% by the age of 70 years. [76,77] Especially, adenomas with villous structures, [78] high grade dysplasia, [78] or 1 cm or larger, [78,79] often develop into colorectal cancer. As a consequence, colorectal cancer is the third most common type of cancer worldwide, [80] and its incidence is still rising. In 2012, 1,361,000 new patients with colorectal cancer were globally diagnosed, while 694,000 patients died from this disease in the same year. [81] In the general population, the overall life-time risk for getting colorectal cancer is ~5%, and this risk only differs slightly between men (5.9%) and women (4.0%). [82,83]

The role of dietary supplements in relation to colorectal cancer risk in the general population has been studied comprehensively in observational prospective and retrospective studies leading to inconsistent associations between supplemental intakes of vitamin A, [84,85] vitamin C, [84-86] vitamin E, [84-87] vitamin D, [84,88-92] calcium, [42-45,84,90,92,93] folic acid, [86,94,95] garlic [96,97] and colorectal cancer risk. Nevertheless, an inverse association was observed for use of multivitamin supplements and risk of colorectal cancer. [94,98-103] Furthermore, abundant observational studies investigated the association between nutrient intakes from foods and supplements combined and colorectal cancer risk in the general population, and results were reviewed and meta-analysed. [104-106] However, in those analyses the separate effects of individual supplements were not taken into account and warrant further attention. Since a systematic literature review with meta-analyses of observational studies investigating the habitual intakes of dietary supplements solely in relation to colorectal cancer risk in the general population is lacking, there is a need to summarize the literature in order

to contribute to uniform conclusions on the association of dietary supplement use and colorectal cancer risk.

Dietary supplement use and colorectal tumor risk in populations at high risk of colorectal cancer

The recommendations for cancer prevention from the WCRF/AICR focus on individuals in the general population who have a relatively low lifetime risk of developing colorectal cancer. Important gaps of knowledge exist with regard to dietary supplement use and colorectal tumor incidence and recurrence in high-risk populations for colorectal tumors, i.e. those with a history of sporadic colorectal adenomas, those with Lynch syndrome, and patients diagnosed with colorectal cancer. These gaps stress the need to get more insight into the role of dietary supplement use and colorectal tumor risk and recurrence among those high-risk populations.

Individuals with sporadic colorectal adenomas

Approximately 15–40% of individuals with a history of sporadic colorectal adenomas develop recurrent colorectal adenomas within three years after polypectomy. [107] As most colorectal cancers develop via the adenoma-carcinoma pathway, those individuals are at higher risk for colorectal cancer. [74] According to one study, the cumulative risk of colorectal cancer among individuals with large polyps (>1 cm) was 2.5%, 8% and 24% at 5, 10 and 20 years respectively. [108] Based on knowledge of an increased risk of colorectal cancer, individuals diagnosed with colorectal adenomas may have changed their use of dietary supplements after polypectomy. [109] However, no specific recommendations exist for lifestyle changes after diagnosis of a colorectal adenoma. [110,111] Therefore, dietary supplement use in individuals with a history of sporadic colorectal adenomas might be similar to use in the general population. [1]

Few randomized controlled trials, with colorectal tumors as secondary outcomes, investigated the role of individual dietary supplements in recurrent sporadic colorectal tumors showing that there is substantial evidence to support that use of calcium supplements significantly reduced the risk of recurrent adenomas. [112] However, no protection was observed for use of folic acid supplements against recurrence of colorectal adenomas according to meta-analyses of interventional trials. [49,113] Up to now, evidence for the association between recurrent colorectal adenomas and the habitual intake of

commonly used dietary supplements is lacking as the dosage and composition of dietary supplements in trials are fixed. In order to gain more insight into the association between habitual dietary supplement use and colorectal adenoma recurrence as a primary outcome among individuals with a history of sporadic colorectal adenomas, more evidence from observational studies is needed.

Individuals with Lynch syndrome

Lynch syndrome, which is caused by pathogenic germline mutations in one of the DNA mismatch repair (MMR) genes, i.e. MLH1, MSH2, MSH6, PMS2, [114-120] or the EPCAM gene, [119,120] is the most common hereditary form of colorectal cancer, [121,122] and is thought to be responsible for approximately 3% of the total burden of colorectal cancer. [121,122] A fast progression of the adenoma-carcinoma sequence at a younger age [123,124] is often seen in individuals with Lynch syndrome, and those individuals have a substantially higher risk for colorectal cancer ranging from 25–70% up to age 70 compared to the lifetime risk of 2–5% in the general population. [115-118,125]

Currently, the prevalence of dietary supplement use among individuals with Lynch syndrome has not been explored yet. However, in order to prevent acute or chronic disease, those individuals might have a higher use of dietary supplements compared to the general population as they are aware of their health status and familial risk. [109] So far, only few studies have evaluated the role of diet [126-128] and lifestyle [128-130] in the development of colorectal tumors in individuals with Lynch syndrome, showing that the established risk factors of colorectal cancer, such as smoking, [130] overweight, [129] and westernized dietary habits, [126] may be especially detrimental in those with Lynch syndrome. However, due to the high lifetime risk for colorectal cancer, these individuals may be willing to learn about strategies for managing high cancer risk, [131] and may also be motivated to making changes in health behavior, [132,133] including dietary supplement use. To the best of our knowledge, the association between dietary supplement use and colorectal tumor risk in individuals with Lynch syndrome has not been studied yet.

Individuals with colorectal cancer

Currently, colorectal cancer is commonly diagnosed, [80,134] and prognosis is depending on disease stage at diagnosis. [135] Approximately 20% of the colorectal cancer patients will develop metastases during follow-up, [134] and the 5-years survival rates vary from ~80% in stage I to <5% in stage IV. [135] Despite advances in chemotherapy and surgical techniques,

the recurrence rate of colorectal tumors increases as the stage of the cancer advances. [136] Almost half of all colorectal cancer patients will develop recurrent disease of which ~25% includes patients with disease stage I and II. [137]

It is still unclear whether use of dietary supplements by colorectal cancer patients affects colorectal cancer recurrence and survival. So far, only one study investigated the association between dietary supplement use and colorectal cancer recurrence and survival, and showed that multivitamin use during and after adjuvant chemotherapy was not significantly associated with recurrence or survival in observational analyses of stage III colon cancer patients (n=1,038) who were originally enrolled in a randomized adjuvant chemotherapy trial. [138] That study assessed dietary supplement use during and six months after adjuvant chemotherapy, but no information about use was available at diagnosis and several years post-diagnosis. Furthermore, in other studies, dietary supplement use was assessed at one point in time assuming that use after diagnosis, during or after cancer therapy is stable. However, it is plausible that dietary supplement use may vary after diagnosis and during or after cancer therapy, and use may not necessarily be beneficial since supplements could interact with conventional cancer treatments. [64-67,139-141]

In order to prevent recurrence of the disease and to improve well-being and prognosis, colorectal cancer patients might take dietary supplements directly after diagnosis, [142,143] during or after cancer therapy. [14,63,143-145] Also, they often report to start taking additional dietary supplements. [12,142] It has been estimated that about 60–80% of the colorectal cancer patients use dietary supplements already before diagnosis, [146] while use during, [14,63] or after cancer therapy [144,145] varies between 38–45%. In addition, it has been suggested that around 20% of the patients start taking dietary supplements after colorectal cancer diagnosis, [62,144] while around 24% of the colorectal cancer patients, who used dietary supplements before diagnosis, quit use several years post-diagnosis. [144,145] These findings suggest that variations in dietary supplement use over time after colorectal cancer diagnosis and during or after cancer therapy may be present. Thus, before associations between dietary supplement use and recurrence and survival in colorectal cancer patients can be examined, more information is needed about the consistency of use over time among individuals with established colorectal cancer as there is a deficit in knowledge about this issue.

Outline of the thesis

The overall aim of this thesis is to improve our knowledge about the role of dietary supplement use in colorectal tumor development in the general population and in populations at high risk for colorectal tumors, i.e. colorectal adenomas or carcinomas, and to gain insight into the consistency of dietary supplement use over time in patients diagnosed with colorectal cancer. For this purpose, we conducted a systematic literature review and meta-analyses of prospective cohort studies in the general population on the association between dietary supplement use and colorectal cancer risk (**chapter 2**). In **chapter 3**, the association between dietary supplement use and recurrence of colorectal adenomas has been examined in a prospective cohort study among sporadic colorectal adenoma patients – the POLIEP follow-up study. The association between dietary supplement use and colorectal tumor risk in a prospective cohort study among individuals with Lynch syndrome – the GeoLynch cohort study – has been investigated in **chapter 4**. The rationale and design of the prospective cohort study among colorectal cancer patients – the COLON study – has been described in **chapter 5**. Within the COLON study, the consistency of dietary supplement use in colorectal cancer patients at diagnosis, during cancer therapy and several years post-diagnosis has been explored (**chapter 6**). This thesis concludes with a discussion of the results from all studies included in this thesis, and also points out recommendations for public health and clinical practice and several future research opportunities (**chapter 7**).

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Chapter 2

Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies

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ABSTRACT

Background Use of dietary supplements is rising in countries where colorectal cancer is prevalent. We conducted a systematic literature review and meta-analyses of prospective cohort studies on dietary supplement use and colorectal cancer risk.

Methods and materials We identified relevant studies in Medline, Embase and Cochrane up to January 2013. Original and peer-reviewed papers on dietary supplement use and colorectal cancer, colon cancer, or rectal cancer incidence were included. 'Use-no use' (U-NU), 'highest-lowest' (H-L), and 'dose-response' (DR) meta-analyses were performed. Random-effects models were used to estimate summary RRs and 95% CIs.

Results In total, 24 papers were included in the meta-analyses. We observed inverse associations for colorectal cancer risk and multivitamins (U-NU: RR=0.92; 95% CI 0.87–0.97) and calcium supplements (U-NU: RR=0.86; 95% CI 0.79–0.95; H-L: RR=0.80; 95% CI 0.70–0.92; DR: for an increase of 100 mg/day, RR=0.96; 95% CI 0.94–0.99). Inconsistent associations were found for colon cancer risk and use of supplemental vitamin A and vitamin C, and for colorectal cancer risk and use of supplemental vitamin D, vitamin E, garlic, and folic acid.

Conclusion Meta-analyses of observational studies suggest a beneficial role for use of multivitamins and calcium supplements on colorectal cancer risk, while the association with other supplements and colorectal cancer risk is inconsistent. Residual confounding of lifestyle factors might be present. Before recommendations can be made, an extensive assessment of dietary supplement use and a better understanding of underlying mechanisms is needed.

INTRODUCTION

Diet and lifestyle play a role in colorectal cancer development. [1-3] The 'Food, Nutrition, Physical activity, and the prevention of cancer: a global perspective' Report in 2007, [4] and the 'Continuous Update Project Report on colorectal cancer' in 2011 [5] of the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) concluded that red and processed meat, alcoholic drinks among men, high body and abdominal fatness, and adult attained height increase the risk for colorectal cancer, while foods containing dietary fiber and being physically active decrease the risk for colorectal cancer. [5] However, no conclusions about the evidence on dietary supplement use and colorectal cancer risk could be made as too few studies were available to show consistent associations. Since use of dietary supplements is rising in countries where colorectal cancer is prevalent, it is of great relevance to summarize the evidence between dietary supplement use and colorectal cancer risk.

Several randomized trials on dietary supplement use and chronic diseases have been conducted. The primary endpoints in those trials were cardiovascular diseases, osteoporosis, and (overall) cancer, [6-9] but not colorectal cancer. Moreover, in those trials very specific subgroups, e.g. postmenopausal women, [10,11] heavy smokers, [12,13] health professionals, [14-16] and populations at high risk for cancer [14,17,18] and cardiovascular diseases [19,20] were studied, which makes it difficult to generalize the results to the general population. According to meta-analyses conducted on the results of these trials, supplemental antioxidants, [6,7] folic acid, [9] and calcium [8] did not significantly influence colorectal cancer risk.

To the best of our knowledge, no systematic review and meta-analyses of prospective cohort studies have been conducted that focus on colorectal cancer risk and use of dietary supplements specifically. Pooled analyses from 13 cohort studies on total intakes or intakes from foods only, but not solely from supplements, of vitamins A, C, E, and folate showed modest inverse associations on colon cancer risk. [21,22] A statistically significant inverse association was also found for multivitamin use and colon cancer risk. [21] In addition, a pooled analysis of 10 cohort studies showed that total calcium intake was inversely associated with colorectal cancer risk. [23]

We conducted a systematic review and meta-analyses of prospective cohort studies on dietary supplement use and colorectal cancer risk up to January 2013. Because of the abundant prospective data from cohort studies and potential recall bias from case-control studies, case-control studies were not summarized.

METHODS AND MATERIALS

Search strategy

The present systematic literature review has been carried out according to the guidelines of the WCRF. [24] The search strategy identified several terms on dietary supplement use and colorectal cancer risk, and yielded studies with outcomes on colorectal adenomas and colorectal carcinomas as it was part of a larger research project. As the current study focuses on colorectal carcinomas only, studies on colorectal adenomas were excluded. We retrieved relevant articles by searching in Medline, Embase, and Cochrane from their inception up to January 2013, and hand-searched reference lists for additional studies (**Supplemental material 2.1**). No language restrictions were made.

Study selection

We included prospective cohort studies if they reported original and peer-reviewed data on the association of dietary supplement use and colorectal, colon, or rectal cancer incidence. To be included in the meta-analyses, information on ascertainment of colorectal cancer cases, and estimates of the relative risk with 95% confidence interval (95% CI) were required in the publication. When we identified multiple papers on the same study, we selected the publication with the largest number of cases, a longer follow-up, and completeness of the information.

Data extraction

From each relevant study, information on study characteristics, number of cases, follow-up period, cancer site, description of dietary supplement use, relative risks (RRs) and 95% CIs, and details of the adjustment for confounders were extracted and stored in a database. The literature search (RHB, RW, LK, AOL, ET), data selection (RHB, RW, LK, AOL, ET), and data extraction (RHB, LK, AOL, ET) were performed independently by several reviewers at Wageningen University, Wageningen, the Netherlands.

Statistical analyses

Random effects models were used to calculate summary RRs and 95% CIs for the associations of colorectal, colon or rectal cancer risk with use of multivitamins, vitamin A, vitamin

C, vitamin D, vitamin E, calcium, folic acid, and garlic supplements. [25] We performed a meta-analysis if at least two cohort studies were available. We used the most fully adjusted relative risk in the analysis.

'Use-no use' meta-analyses were done for the association between use of multivitamins, supplemental vitamin A, vitamin C, vitamin D, vitamin E, calcium, and garlic with colorectal cancer risk. In those meta-analyses, 'no use' incorporates either 'never use', 'no current use', and/or 'no past use'. In addition, 'use' was defined as 'current use', 'past use' and/or 'any use'. Studies that focused on current use of dietary supplements only, and reported on specified categories of dietary supplement use were included in the 'highest-lowest' meta-analyses. In those analyses, we always compared the highest versus the lowest category of intake, and did not include the middle categories, and we included the association as reported in the original publication, which could be tertiles, quartiles, or quintiles. Details about the contrasts between categories in the original publications can be found in **Table 2.1**. For the association between use of supplemental vitamin A, vitamin C, vitamin D, vitamin E, calcium and folic acid and colorectal cancer risk, 'highest-lowest' meta-analyses were conducted. In the 'dose-response' meta-analyses, we tested whether there was a linear association between the dosage of a supplement and colorectal cancer risk: thus, in those analyses we could only include studies that provided information on the dosage of intake. According to the DerSimonian and Lard method, [25] 'dose-response' meta-analyses were possible for the association between vitamin C, vitamin D, vitamin E, calcium, and folic acid supplement use and colorectal cancer risk, and were carried out when three or more categories of the dosage of intake of the dietary supplement were available. We used the method of Greenland and Longnecker to compute the trend across categories of exposure. [26] We estimated the distribution of cases or person-years in studies that did not report these, and reported results by quantiles. [27]

The median level of exposure in each category was used for the corresponding relative risk. If not reported, the value assigned was the midpoint of the lower and upper bound in each category. For open-ended categories, the midpoint was calculated by adding or subtracting half the width of the adjacent exposure category for the uppermost or lowermost category respectively. For studies that reported supplement use in ≥3 categories, [28-37] we calculated a combined estimate of dietary supplement use by using Hamling's procedure before including the study in the overall analysis. [38] For studies that reported results for men and women separately, [33,34,39] and for studies that showed separate results for colon and rectal cancer risk, [32,40] we used fixed effect meta-analyses to obtain an overall estimate for overall gender and for colorectal cancer risk respectively.

Table 2.1 Publications on dietary supplement use and colorectal cancer risk included in the meta-analyses

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Zhang, 2006, Women's Health Study, USA [29]	Cohort (N=37,916) 10 years Women 220 CRC cases Age: ≥45	Self-report Medical records	Multivitamins	Status*, CRC	Never use vs Past use	0.94	0.64–1.37	1, 3, 4, 5, 6, 7, 8, 9, 10, 13	X		
					Never vs Current use	1.07	0.72–1.61		X		
Jacobs, 2003, Cancer Prevention Study II Nutrition Cohort, USA, [28]	Cohort (N=145,260) 5 years Men and women 797 CRC cases Age: ≥30	Self-report Medical records	Multivitamins	Recent use in 1992-1993, CRC	No past & recent use vs Occasional use (1–3x/week)	0.73	0.44–1.19	1, 2, 4, 5, 10, 14	X		
					No past & recent use vs Regular use (≥4x/week)	1.04	0.87–1.23		X		
Neuhouser, 2009, Women's Health Initiative, USA, [59]	Cohort (N=161,808) 8 years Women 1,590 CRC cases Age: 50–79	Self-report Medical records	Multivitamins	Any use at least 1x per week, CRC	No vs Yes	0.99	0.88–1.11	1, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14	X		
Sanjoaquin, 2004, Oxford Vegetarian Study, UK, [58]	Cohort (N=10,998) 17 years Men and women 95 CRC cases Age: 16–89	Population registry	Multivitamins	Use*, CRC	No use vs Use	1.00	0.63–1.59	1, 2, 7, 8	X		

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
McCarl, 2006, Iowa Women's Health Study, USA, [57]	Cohort (N=35,197) 14 years Women 954 CRC cases Age: 55–69	Cancer registry Population registry	Multivitamins	Use over the past year, CRC	No vs Yes	0.82	0.71–0.94	1	X		
Park, 2011, Multiethnic Cohort Study, USA, [56]	Cohort (N=182,099) 11 years Men and women 1,494 CRC cases (men) 1,292 CRC cases (women) Age: 45–75	Cancer registry Population registry	Multivitamins	Use at least 1x per week over the last year at baseline and during 5yrs FU, CRC	No use vs Use at both time points (men)	1.08	0.66–1.75	1, 3, 4, 5, 7, 8, 9, 10, 13, 14	X		
					No use vs Use at both time points (women)	0.71	0.43–1.18		X		
Lee, 2011, Nurses' Health Study * Health Professionals Follow-up Study, USA, [30]	Cohort (N=135,151) 24 years Men and women 2,295 CRC cases Age: 30–75	Self-report Medical records	Multivitamins	Duration of use[$], CRC	Never vs Past use	0.99	0.82–1.21	1, 3, 4, 5, 6, 7, 8, 9, 10, 13	X		
					Never vs Current use 1–5 y	0.96	0.81–1.13		X		
					Never vs Current use 6–9 y	0.89	0.75–1.06		X		

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
					Never vs Current use 10–15 y	0.89	0.76–1.05		X		
					Never vs Current use 16–19 y	0.71	0.53–0.96		X		
					Never vs Current use ≥20 y	0.77	0.64–0.94		X		
			Folic acid	Cumulative average of past and recent use of synthetic folic acid from fortification and supplementation, CRC	<50 vs 50–<100 mcg/day	0.89	0.77–1.02			X	
					<50 vs 100–<200 mcg/day	0.97	0.86–1.10			X	
					<50 vs 200–<400 mcg/day	0.89	0.78–1.00			X	
					<50 vs ≥400 mcg/day	0.93	0.81–1.06			X	X

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders¥	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Shibata, 1992, Leisure World Study, USA, [39]	Cohort (N=11,580) 8 years Men and women 97 CC cases (men) 105 CC cases (women) Age: 65–84	Medical records	Vitamin A	Current use at least 1x per week, CC	No vs Yes (10,000 IU/ day, men)	0.99	0.66–1.49	1, 7	X		X
					No vs Yes (10,000 IU/ day, women)	0.63	0.42–0.94		X		X
			Vitamin C	Current use at least 1x per week*, CC	No vs Yes (500 mg/day, men)	0.92	0.62–1.38		X		X
					No vs Yes (500 mg/day, women)	0.67	0.45–0.99		X		X
			Vitamin E	Current use at least 1x per week*, CC	No vs Yes (200 IU/day, men)	1.01	0.68–1.51		X		X
					No vs Yes (200 IU/day, women)	0.76	0.52–1.12		X		X

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Sellers, 1998, Iowa Womens's Health Study, USA, [31]	Cohort (N=35,216) 10 years Women 241 CC cases without family history of CRC Age: 55–69	Cancer registry	Vitamin A	Use over the past year, CC	0 vs ≤5,000 IU/day	0.70	0.50–1.10	1, 9	X		
					0 vs >5,000 IU/day	0.80	0.50–1.30		X		X
			Vitamin C	Use over the past year, CC	0 vs ≤180 mg/day	0.70	0.50–1.10		X	X	X
					0 vs >180 mg/day	0.70	0.50–1.40		X	X	
			Vitamin E	Use over the past year, CC	0 vs ≤30 mg/day	0.80	0.10–1.20		X	X	X
					0 vs >30 mg/day	0.60	0.40–0.90		X	X	
			Vitamin D	Use over the past year, CC	0 vs ≤400 IU/day	0.60	0.40–0.90		X	X	X
					0 vs >400 IU/day	0.80	0.50–1.30		X	X	
			Calcium	Use over the past year, CC	0 vs ≤500 mg/day	0.70	0.50–0.90		X	X	X
					0 vs >500 mg/day	0.60	0.40–0.90		X	X	

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders¥	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Roswall, 2010, Diet Cancer and Health Study, Denmark, [32]	Cohort (N=56,332) 10.6 years Men and women 465 CC cases 283 RC cases Age: 50–64	Cancer registry	Vitamin C	Supplemental intake during the last year, CC	Per 100 mg vitamin C	1.00	0.95–1.04	4, 5, 7, 8, 10, 13, 14		X	
					0 vs ≤39.96 mg	1.18	0.82–1.70		X		
					0 vs >39.96–≤60.00 mg	1.27	0.86–1.87		X		
					0 vs >60.00 mg	1.05	0.73–1.49		X		X
			Vitamin E	Supplemental intake during the last year, CC	Per 10 mg vitamin E	1.01	1.00–1.03			X	
					0 vs ≤6.66 mg	0.93	0.64–1.36		X		
					0 vs >6.66–≤10 mg	1.05	0.70–1.57		X		
					0 vs >10 mg	1.06	0.73–1.56		X		X
			Folic acid	Supplemental folic acid during the last year, CC	Per 100 mcg folate	1.01	0.96–1.06			X	
					0 vs >0–≤83.2 mcg	0.79	0.55–1.13		X		
					0 vs >83.2–≤142.8 mcg	0.90	0.61–1.30		X		
					0 vs >142.8 mcg	0.83	0.58–1.20		X		X

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Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders¥	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
				Supplemental folic acid during the last year, RC	Per 100 mcg folate	0.98	0.97–1.06			X	
					0 vs >0–≤83.2 mcg	0.56	0.34–0.91		X		
					0 vs >83.2–≤142.8 mcg	0.82	0.51–1.33		X		
					0 vs >142.8 mcg	0.60	0.36–0.99		X		X
Wu, 2002, Nurses' Health Study & Health Professionals Follow-up Study, USA, [63]	Cohort NHS (N=87,998) 18 years Women 626 CC cases Age: 30–55	Self-report Medical records	Vitamin E	Use during the last year, CC	Never use vs Vitamin E pills only	0.80	0.54–1.19	1, 3, 5, 7, 6, 8, 10, 13	X		
				Vitamin E supplementation from vitamin E pills only, CC	Never use vs ≤250 IU	0.95	0.65–1.39			X	
					Never use vs 300–500 IU	0.90	0.66–1.22			X	
					Never use vs ≥600 IU	0.78	0.43–1.42			X	X
	Cohort HPFS (N=47,344) 8 years Men 399 CC cases Age: 40–75			Use during the last year, CC	Never use vs Vitamin E pills only	0.79	0.46–1.34		X		

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
				Vitamin E supplementation from vitamin E pills only, CC	Never use vs ≤250 IU	1.09	0.72–1.64			X	
					Never use vs 300–500 IU	0.73	0.52–1.03			X	
					Never use vs ≥600 IU	0.70	0.38–1.29			X	X
Lin, 2005, Women's Health Study, USA, [37]	Cohort (N=36,976) 10 years Women 223 CRC cases Age: ≥45	Self-report Medical records	Vitamin D	Use during the last year, CRC	0 vs >0–400 IU/day	1.36	0.95–1.95	1, 3, 4, 5, 7, 8, 9, 10, 13	X		X
			Calcium	Use during the last year, CRC	0 vs >0–499 mg/day	0.98	0.70–1.38		X	X	
					0 vs ≥500 mg/day	1.30	0.90–1.87		X	X	X
Martinez, 1996, Nurses' Health Study, USA, [61]	Cohort (N=89,448) 12 years Women 501 CRC cases Age: 30–55	Self-report Medical records	Vitamin D	Use during the last year, CRC	No use vs Use	0.95	0.79–1.15	1, 3, 4, 5, 6, 7, 8, 10	X		
Kearney, 1996, Health Professionals Follow-up Study, USA, [62]	Cohort (N=47,935) 6 years Men 203 CC cases Age: 40–75	Self-report Medical records	Vitamin D	Supplementary vitamin D during the last year, CC	<4.0 vs 4.0–86 IU/day	1.12	0.70–1.79	1, 3, 4, 5, 6, 7, 8, 9, 10		X	

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Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
					< 4.0 vs 87–342 IU/day	0.55	0.26–1.18			X	
					< 4.0 vs 343–447 IU/day	0.87	0.59–1.27			X	
					< 4.0 vs ≥448 IU/day	0.48	0.22–1.02			X	X
Park, 2007, Multiethnic Cohort Study, USA, [33]	Cohort (N=191,011) 7.3 years Men and women 2,110 CRC cases Age: 45–75	Cancer registry	Vitamin D	Supplemental vitamin D at least weekly during the last year, CRC	0 vs 1–≤400 IU/day (men)	0.92	0.80–1.06	1, 3, 4, 5, 6, 7, 9, 10, 12	X	X	
					0 vs >400 IU/day	0.65	0.49–0.84		X	X	X
					0 vs 1–≤400 IU/day (women)	0.98	0.84–1.15		X	X	
					0 vs >400 IU/day	0.97	0.75–1.26		X	X	X
			Calcium	Supplemental calcium at least weekly during the last year, CRC	0 vs 1–<200 mg/day (men)	0.94	0.81–1.09		X	X	
					0 vs ≥200 mg/day	0.74	0.60–0.90		X	X	X
					0 vs 1–<200 mg/day (women)	1.00	0.84–1.20		X	X	

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders¥	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
					0 vs ≥200 mg/day	0.82	0.69–0.98		X	X	X
Järvinen, 2001, Finnish prospective cohort study, Finland, [60]	Cohort (N=9,959) 24 years Men and women 72 CRC cases Age: ≥15	Cancer registry	Vitamin D	Use*, CRC	No use vs Use		0.08–4.22	1, 2, 4, 7, 11, 9, 10,	X		
Flood, 2005, Breast Cancer Detection Demonstration Project, USA, [35]	Cohort (N=45,354) 8.5 years Women 482 CRC cases Average age: 61.9	Cancer registry Population registry	Calcium	Supplemental calcium during the last year, CRC	0 vs 0–400 mg/day	1.08	0.87–1.34	1	X	X	
					0 vs 401–800 mg/day	0.96	0.70–1.32		X	X	
					0 vs >800 mg/day	0.76	0.56–1.02		X	X	X
Park, 2009, NIH-AARP Diet and Health Study, USA, [34]	Cohort (N=492,810) 7 years Men and women 5,098 CRC cases Age: 50–71	Cancer registry	Calcium	Supplemental calcium during the last year, CRC	0 vs >0–<400 mg/day (men)	0.96	0.88–1.05	3, 4, 5, 7, 8, 9, 10, 12, 14	X	X	
					0 vs 400–<1000 mg/day	0.91	0.79–1.04		X	X	
					0 vs ≥1,000 mg/day	0.74	0.58–0.94		X	X	X

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
					0 vs >0–<400 mg/day (women)	1.02	0.89–1.17		X	X	
					0 vs 400–<1000 mg/day	0.86	0.73–1.00		X	X	
					0 vs ≥1,000 mg/day	0.86	0.72–1.02		X	X	X
McCullough, 2003, Cancer Prevention Study II Nutrition Cohort, USA, [36]	Cohort (N=127,749) 5 years Men and women 683 CRC cases Age: 50–74	Self-report Medical records	Calcium	Supplemental calcium during the last year, CRC	0 vs 1–499 mg/day	0.71	0.52–0.96	1, 3, 4, 5, 7, 9, 10, 14		X	
					0 vs ≥500 mg/day	0.69	0.49–0.96			X	X
					No use vs Use (pooled)	0.70	0.56–0.88		X		
Kampman, 1994, Netherlands Cohort Study, the Netherlands, [66]	Casecohort (N=120,852) 3.3 years Men and women 326 CRC cases Age: 55–69	Cancer registry Pathology registry	Calcium	Use*, CRC	No use vs Use	0.95	0.50–1.78	1, 3, 7, 9, 10, 14	X		

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders¥	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Wu, 2002, Nurses' Health Study & Health Professionals Follow-up Study, USA, [65]	Cohort (N=135,342) 16 years Men and women 1,025 CRC cases Age: 30–75	Self-report Medical records	Calcium	Supplemental calcium during the last year, CRC	Never users vs Current users*	0.69	0.51–0.94	1, 3, 4, 5, 6, 7, 8, 10, 13	X		
Stevens, 2011, Cancer Prevention Study II Nutrition Cohort, USA, [64]	Cohort (N=99,523) 8 years Men and women 1,023 CRC cases Age: 50–74	Self-report Medical records	Folic acid	Folic acid from fortification and supplementation during the last year, CRC	<101 vs 101–<182 mcg/day	1.03	0.86–1.24	1, 2, 3, 4, 6, 7, 8, 9, 10		X	
					<101 vs 182–<452 mcg/day	0.95	0.78–1.16			X	
					<101 vs 452–<560 mcg/day	0.96	0.79–1.18			X	
					<101 vs ≥560 mcg/day	0.84	0.68–1.03			X	X
Satia, 2009, VITamins AND Lifstyle study, USA, [67]	Cohort (N=76,512) 5 years Men and women 428 CRC cases Age: 50–76	Population registry	Garlic	Any use over the previous 10 years, CRC	No use vs Any use over the previous 10 years	1.35	1.01–1.81	1, 2, 4, 5, 6, 10, 14	X		

Table 2.1 continues on next page

Table 2.1 *Continued*

Author, year, study, country	Study characteristics	Case ascertainment	Supplement	Exposure details, outcome	Exposure categories/ increment	RR	95% CI	Con-founders[¥]	Use-no use meta-analysis	Dose-response meta-analysis	Highest-lowest meta-analysis
Dorant, 1996, Netherlands Cohort Study, the Netherlands, [40]	Casecohort (N=120,852) 3.3 years Men and women 374 CRC cases Age: 55–69	Cancer registry Pathology registry	Garlic	Garlic supplement use for at least one year during the 5 years before baseline, CRC	No use vs Use* (colon)	1.26	0.84–1.91	1, 3, 7, 10, 14	X		
					No use vs Use*(rectum)	0.77	0.41–1.46		X		

[¥] Adjusted for the following confounders: **1.** Age, **2.** Sex, **3.** Family history of CRC, **4.** Body Mass Index, **5.** Physical activity, **6.** NSAID use, **7.** Smoking status, **8.** Alcohol consumption, **9.** Energy intake, **10.** Dietary factors, **11.** Province, **12.** Ethnicity, **13.** Menopausal status (in women only), **14.** Educational level.

* Not further specified.

[$] Calculated on the basis of the reported duration at baseline and updated by subsequent responses to current multivitamin use.

Statistical heterogeneity between studies was assessed by the I^2 statistic. [41,42] Small study bias was examined in funnel plots and by Egger's test. [43] If feasible, stratified analyses were performed for gender, cancer site, or geographical region. Sensitivity analyses were done by excluding one study at a time, and pooling the rest to explore whether a single study could have markedly affected the results.

Statistical analyses were conducted with STATA version 11.0 (StataCorp, College Station, TX, USA). A P-value <0.05 was considered statistically significant.

RESULTS

In total, 81 publications examined the association between dietary supplement use and colorectal cancer risk (**Figure 2.1**). Randomized controlled trials and case-control studies were excluded. In addition, we excluded 12 publications: 8 were superseded by more recent publications, [44-51] 2 published on cancer deaths only, [52,53] 1 reported on the association between vitamin B6 supplement use and colorectal cancer risk [54] and 1 showed results on iron supplement use [55] and colorectal cancer risk: those associations were not found in other publications. We included a total of 24 publications in the present meta-analyses (**Table 2.1**). **Table 2.2** presents the results of 'use-no use', and 'highest-lowest' meta-analyses, whereas 'dose-response' meta-analyses are depicted in **Figure 2.2**. The prevalence, ranges of doses, and exposure categories of publications on dietary supplement use and colorectal cancer risk included in the meta-analyses are given in **Supplementary Table 2.1**. Unless otherwise stated, there was no indication of small study bias with Egger's test, and sensitivity analyses did not substantially modify the findings. Due to limited data it was not possible to stratify for geographical region.

Multivitamin supplements

We observed a statistically significant inverse association between use of multivitamin supplements and colorectal cancer risk based on seven studies in 'use-no use' meta-analyses (**Table 2.2**, RR=0.92; 95% CI 0.87–0.97). [28-30,56-59] No heterogeneity was detected (I^2=4.9%, P=0.39). The current analysis includes 5 out of 13 cohorts from the Pooling Project, [21] while three cohorts of our analysis were not included in the pooled analyses. [56,58,59] A summary estimate of the Pooling Project and the three cohorts combined also showed a statistically significant decreased risk for colorectal cancer in 'use-no use' meta-analysis

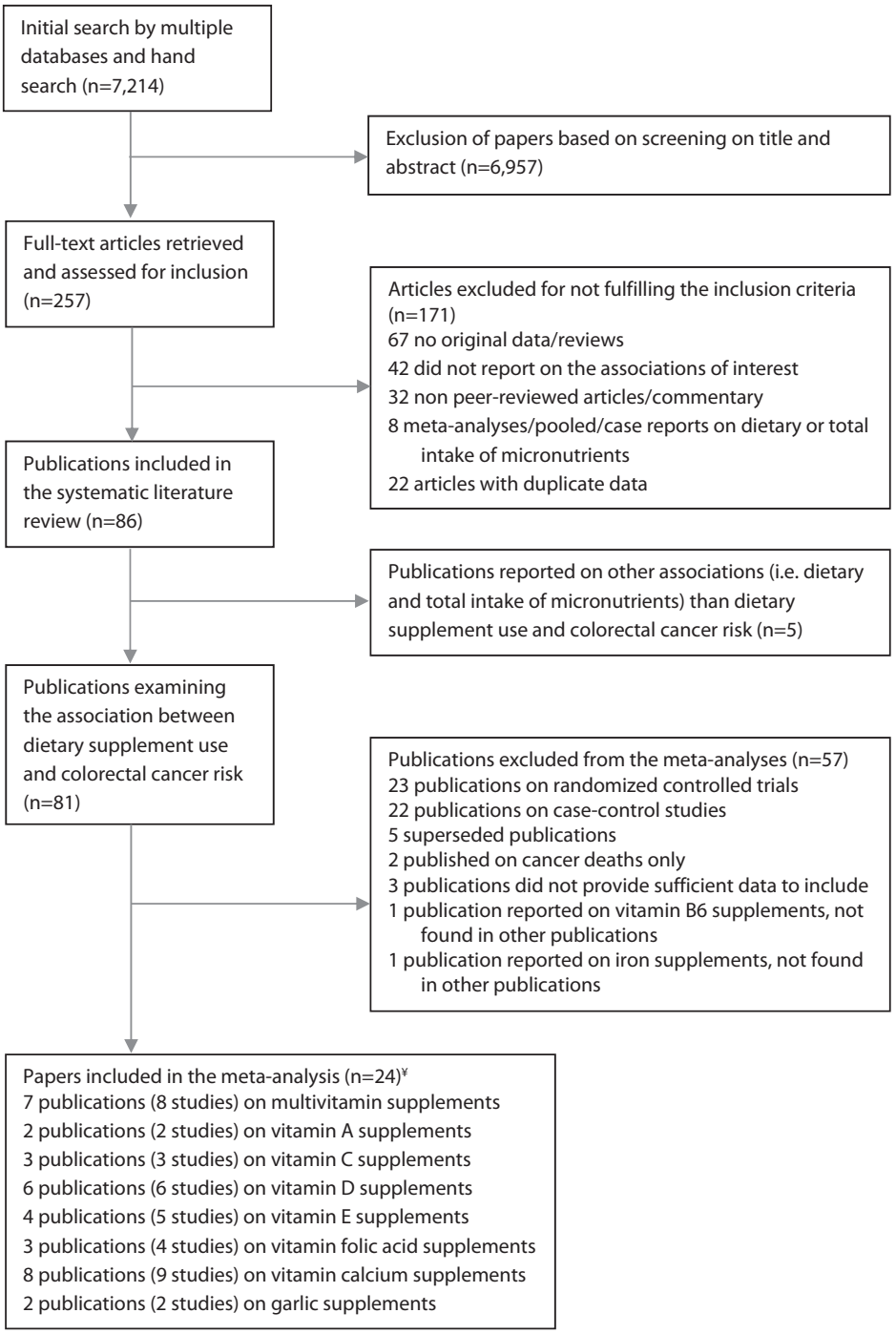


Figure 2.1 Flowchart for study selection for the association of dietary supplement use and colorectal cancer risk (up to January 2013). ¥ Do not add up as most studies included multiple supplements.

of multivitamin supplements (**Table 2.2**, RR=0.92; 95% CI 0.86–0.98). No heterogeneity was present (I^2=0.0%, P=0.43).

Available data for use of multivitamin supplements and colorectal cancer risk were insufficient to conduct 'highest-lowest' and 'dose-response' meta-analyses.

Vitamin A supplements

Based on two studies, [31,39] a statistically significant inverse association was observed for vitamin A supplement use and colon cancer risk in 'use-no use' meta-analysis (**Table 2.2**, RR=0.77; 95% CI 0.62–0.94), whereas this inverse association was borderline statistically significant in 'highest-lowest' meta-analysis (RR=0.79; 95% CI 0.62–1.01). Heterogeneity was not present in either meta-analyses (I^2=0.0%, P=0.76 in 'use-no use' meta-analysis; I^2=0.0%, P=0.97 in 'highest-lowest' meta-analysis). It was not possible to perform 'dose-response' meta-analyses due to limited data.

Table 2.2 Summary relative risks of 'use-no use' meta-analyses and 'highest-lowest' meta-analyses for the association of dietary supplement use and colorectal cancer risk

Dietary supplement	Summary RR	95% CI	I^2, $P_{heterogeneity}$	Included studies	Outcome¥
'Use-no use' meta-analyses					
Multivitamins	0.92	0.87–0.97	4.9%, P=0.39	7 [28-30, 56-59]	CRC
Multivitamins (including Pooling Project)	0.92	0.86–0.98	0.0%, P=0.43	16 [21, 56, 58, 59]	CRC
Vitamin A	0.77	0.62–0.94	0.0%, P=0.76	2 [31, 39]	CC
Vitamin C	0.87	0.63–1.21	77.4%, P=0.01	3 [31, 32, 39]	CC
Vitamin E	0.85	0.72–1.01	20.0%, P=0.29	5 [31, 32, 39, 63]	CC
Vitamin D	0.92	0.78–1.09	53.9%, P=0.07	5 [31, 33, 37, 60, 61]	CRC
Calcium	0.86	0.79–0.95	63.7%, P=0.01	8 [31, 33-37, 65, 66]	CRC
Garlic	1.24	0.99–1.54	0.0%, P=0.34	2 [40, 67]	CRC
'Highest-lowest' meta-analyses					
Vitamin A	0.79	0.62–1.01	0.0%, P=0.97	2 [31, 39]	CC
Vitamin C	0.85	0.68–1.05	10.9%, P=0.33	3 [31, 32, 39]	CC
Vitamin E	0.82	0.67–0.99	11.0%, P=0.34	5 [31, 32, 39, 63]	CC
Vitamin D	0.87	0.62–1.22	67.1%, P=0.03	4 [31, 33, 37, 62]	CRC
Calcium	0.80	0.70–0.92	49.2%, P=0.08	6 [31, 33-37]	CRC
Folic acid	0.88	0.78–0.98	6.2%, P=0.34	3 [30, 32, 64]	CRC

¥ When different outcomes were described between studies (e.g. colorectal cancer, colon cancer, or rectal cancer), we reported the outcome as colorectal cancer.

Vitamin C supplements

We did not observe a statistically significant association for use of vitamin C supplements and colon cancer risk in 'use-no use' (**Table 2.2**, RR=0.87; 95% CI 0.63–1.21) and 'highest-lowest' meta-analysis (RR=0.85; 95% CI 0.68–1.05) based on three studies. [31,32,39] Heterogeneity was high in the 'use-no use' meta-analysis (I^2=77.4%, P=0.01). It was not possible to conduct stratified analyses to explore heterogeneity due to limited data. One study was conducted in Denmark, [32] while the other two studies were performed in the United States. [31,39] When we excluded the study from Denmark in sensitivity analyses, [32] we observed a statistically significant decreased risk for vitamin C supplement use and colon cancer risk and heterogeneity was no longer present (RR=0.74; 95% CI 0.60–0.92, I^2=0.0%, P=0.62). In the 'highest-lowest' meta-analysis a low statistical heterogeneity was detected (I^2=10.9%, P=0.33).

'Dose-response' meta-analysis were based on two studies. [31,32] We did not observe an association between use of supplemental vitamin C and colon cancer risk for an increase of 100 mg/day (RR=0.94; 95% CI 0.78–1.12, **Figure 2.2A**). A high heterogeneity was present (I^2=65.3%, P=0.09). However, we were not able to explore possible sources of heterogeneity due to the limited number of studies.

Vitamin D supplements

Inconsistent associations were observed for use of vitamin D supplements and colorectal cancer risk in all meta-analyses. We included five studies in 'use-no use' meta-analysis, [31,33,37,60,61] and four studies in 'highest-lowest' meta-analysis. [31,33,37,62] 'Use-no use' (RR=0.92; 95% CI 0.78–1.09) and 'highest-lowest' meta-analysis (RR=0.87; 95% CI 0.62–1.22) showed no statistically significant association for use of vitamin D supplements and colorectal cancer risk (**Table 2.2**). In both analyses, heterogeneity was moderate (I^2=53.9%, P=0.07 and I^2=67.1%, P=0.03 respectively). It was not possible to conduct stratified analyses for 'use-no use' meta-analysis. When Lin et al. [37] was excluded in sensitivity analyses heterogeneity was reduced, and a statistically significant decreased risk for vitamin D supplement use and colorectal cancer risk was observed (RR=0.89; 95% CI 0.79–0.99, I^2=21.2%, P=0.28). In 'highest-lowest' meta-analyses, stratified analyses for gender showed a reduced heterogeneity for women (RR=1.04; 95% CI 0.79–1.36, I^2=44.0%, P=0.17) while heterogeneity was no longer present for men (RR=0.63; 95% CI 0.49–0.81, I^2=0.0%, P=0.52).

'Dose-response' meta-analysis were based on three studies. [31,33,62] A statistically significant inverse association was observed for use of supplemental vitamin D and colorectal cancer risk for an increase of 100 mg/day (RR=0.96; 95% CI 0.94–0.99, **Figure 2.2B**). No heterogeneity was present.

Vitamin E supplements

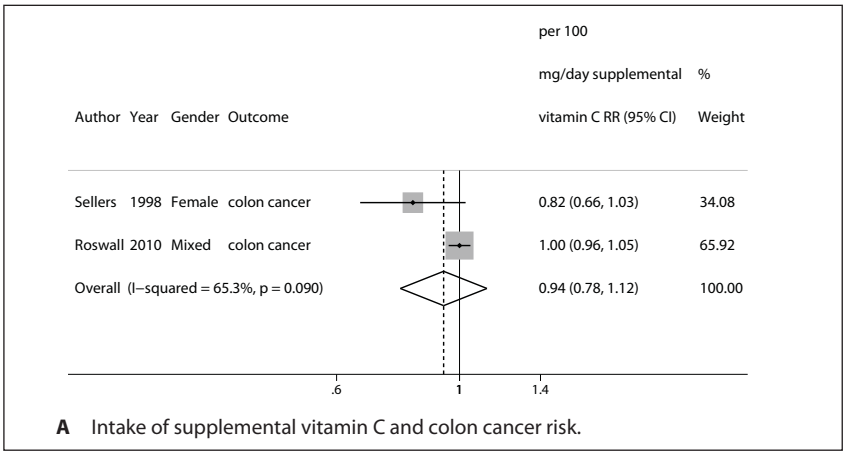
Our analyses showed inconsistent results for use of supplemental vitamin E and colon cancer risk. Based on five studies, [31,32,39,63] we observed a borderline statistically significant inverse association for use of supplemental vitamin E and colon cancer risk in 'use-no use' meta-analysis (RR=0.85; 95% CI 0.72–1.01) while in 'highest-lowest' meta-analysis this inverse association was statistically significant (RR=0.82; 95% CI 0.67–0.99). A low heterogeneity was detected in both analyses (I^2=20.0%, P=0.29 and I^2=11.0%, P=0.34 respectively).

Based on four studies, [31,32,63] 'dose-response' meta-analysis showed no association for an increase of 100 mg/day supplemental vitamin E and colon cancer risk (RR=1.00; 95% CI 0.99–1.01, **Figure 2.2C**). Heterogeneity was high (I^2=69.6%, P=0.02). Due to limited data it was not possible to perform stratified analyses. Sellers et al. [31] only adjusted for age and energy intake, while Wu et al. [63] and Roswall et al. [32] also adjusted for physical activity, smoking, alcohol, dietary factors, and menopausal status. However, sensitivity analyses showed a moderate heterogeneity (I^2=51.4%, P=0.13) when Sellers et al. [31] was excluded, and the association for use of supplemental vitamin E and colon cancer risk did not change (RR=1.00; 95% CI 0.99–1.00).

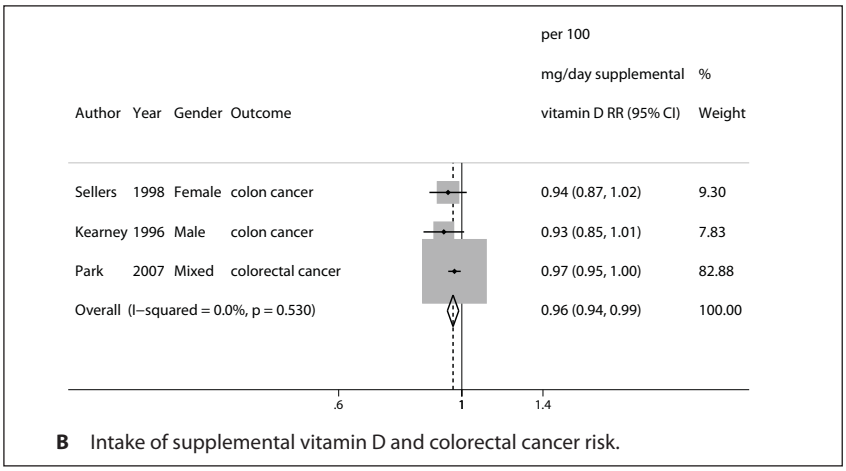
Folic acid from supplements and fortification

Due to insufficient data, we found inconsistent associations for use of supplemental folic acid and colorectal cancer risk. Two studies reported that folic acid intake was calculated by adding the folic acid consumed in fortified foods to that taken as folic acid in individual supplements or multivitamins, [30,64] while no further specification about supplemental intake of folic acid was given by another study. [32] 'Highest-lowest' meta-analysis showed a statistically significant inverse association for use of folic acid from supplements and colorectal cancer risk (**Table 2.2**, RR=0.88; 95% CI 0.78–0.98). [30,32,64] A low statistical heterogeneity was detected (I^2=6.2%, P=0.34). No 'use-no use' meta-analysis could be performed.

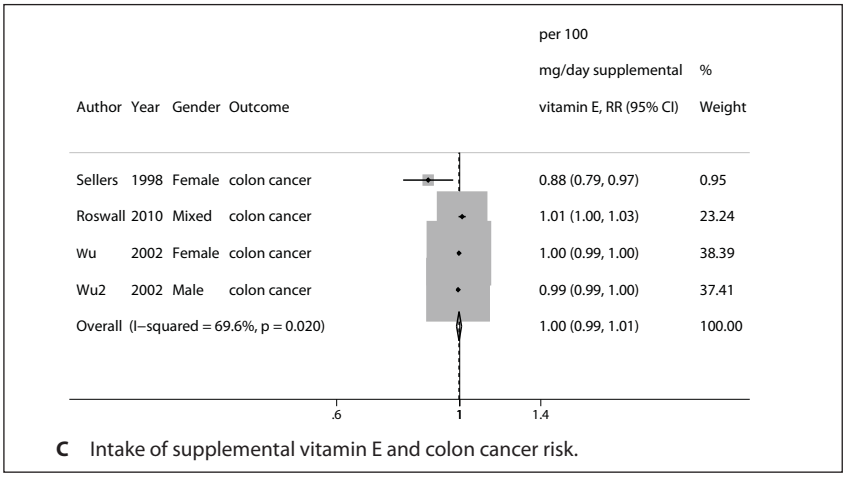
Figure 2.2 'Dose-response' meta-analyses for associations of dietary supplement use and colorectal cancer risk.



A Intake of supplemental vitamin C and colon cancer risk.

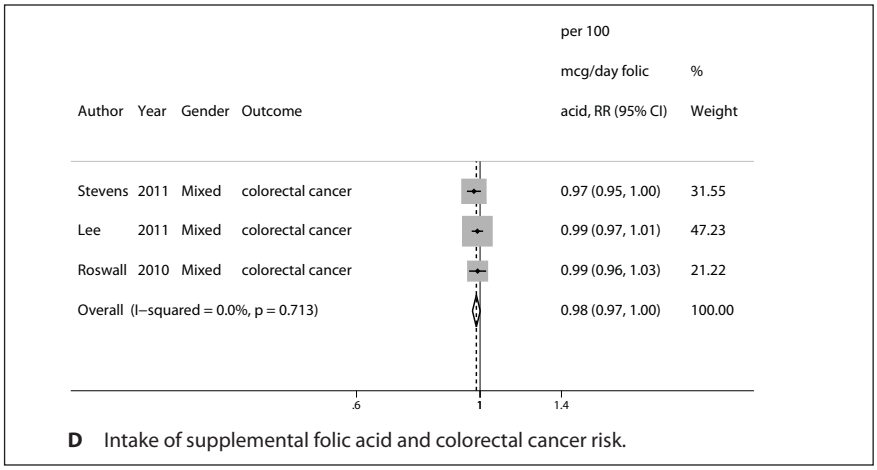


B Intake of supplemental vitamin D and colorectal cancer risk.

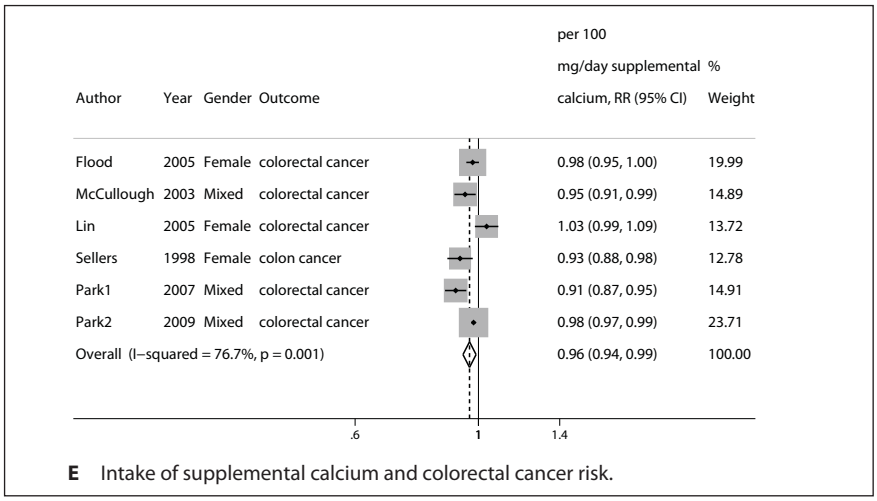


C Intake of supplemental vitamin E and colon cancer risk.

Figure 2.2 *Continued*



D Intake of supplemental folic acid and colorectal cancer risk.



E Intake of supplemental calcium and colorectal cancer risk.

We included three studies in 'dose-response' meta-analysis, [30,32,64] and no association was observed for an increase of 100 µg/day of folic acid from supplements and colorectal cancer risk (RR=0.98; 95% CI 0.97–1.00, **Figure 2.2D**). Heterogeneity was not present (I^2=0.0%, P=0.71).

Calcium supplements

A statistically significant decreased risk for use of calcium supplements and colorectal cancer was found. We included eight studies in 'use-no use' meta-analysis, [31,33-37,65,66] and

six studies in 'highest-lowest' meta-analysis. [31,33-37] A statistically significantly decreased risk for use of calcium supplements and colorectal cancer was observed in 'use-no use' (**Table 2.2**, RR=0.86; 95% CI 0.79–0.95, I^2=63.7%, P=0.01) and in 'highest-lowest' meta-analysis (RR=0.80; 95% CI 0.70–0.92, I^2=49.2%, P=0.08). Heterogeneity was no longer present for colon cancer (RR=0.67; 95% CI 0.56–0.81, I^2=0.0%, P=0.82) when we stratified for cancer site in 'use-no use' meta-analysis, while heterogeneity was reduced for colorectal cancer (RR=0.91; 95% CI 0.86–0.96), I^2=26.9%, P=0.21).

'Dose-response' meta-analysis was based on six studies. [31,33-37] For an increase of 100 mg/day of supplemental calcium, we observed a statistically significant inverse association for use of supplemental calcium and colorectal cancer risk with high heterogeneity (RR=0.96; 95% CI 0.94–0.99, I^2=76.7%, P=0.001, **Figure 2.2E**). Stratified analysis for gender did not reduce heterogeneity (RR=0.97; 95% CI 0.94–1.00, I^2=73.3%, P=0.01 for women; RR=0.95; 95% CI 0.95–1.02, I^2=80.4%, P=0.02 for men). According to sensitivity analyses, heterogeneity was slightly reduced when we excluded Park et al. [33] from the analysis (RR=0.97; 95% CI 0.95–1.00, I^2=65.3%, P=0.02).

Garlic supplements

Based on two studies, [40,67] 'use-no use' meta-analysis showed a non-statistically significant increased risk for garlic supplement use and colorectal cancer (RR=1.24, 95% CI 0.99–1.54). Heterogeneity was not present (I^2=0.0%, P=0.36).

Other supplements

Based on literature, no association was found for use of supplemental beta-carotene and colon (IRR=0.49; 95% CI 0.14–1.71) and rectal cancer risk (IRR=0.87; 95% CI 0.36–2.12). [32] In the Iowa Women's Health Study, [54] a non-statistically significant increased risk for rectal cancer was found for use of vitamin B6 supplements (RR=1.23; 95% CI 0.67–2.25), and a non-statistically decreased risk for colon cancer was observed for selenium supplement use (RR=0.60; 95% CI 0.27–1.32). [49] Supplemental iron was not statistically significantly associated with incident proximal colon cancer and incident distal colon cancer. [55] The relative risks across categories of supplemental iron were 1.0, 1.02, 0.57, 1.10 for proximal colon cancer, and 1.0, 1.09, 1.37, and 1.79 for distal colon cancer. In the VITAL study, [67] any use of glucosamine and chondroitin (HR=0.72; 95% CI 0.54–0.96), fish oil (HR=0.65; 95% CI 0.42–0.99), methylsulfonylmethane

(HR=0.46; 95% CI 0.23–0.93), and St. John's wort (HR=0.35; 95% CI 0.14–0.85) were associated with a statistically significantly lower risk for colorectal cancer, while no associations were observed for use of other herbal and specialty supplements.

DISCUSSION

The present systematic literature review with meta-analyses of prospective cohort studies suggest inverse associations for use of multivitamins and calcium supplements and colorectal cancer risk. Inconsistent associations were found for colon cancer risk and use of supplemental vitamin A and vitamin C, and for colorectal cancer risk and supplemental vitamin D, vitamin E, garlic, and folic acid.

Our results are comparable with pooled analyses of prospective cohort studies. [21-23] Besides for multivitamin use, the pooled data were based on available primary data of prospective cohort studies from foods and supplements combined. Multivitamin supplement use was significantly inversely associated with colon cancer risk in the pooled analyses (RR=0.88; 95% CI 0.81–0.96), [21] and with colorectal cancer risk in the current study. This statistically significant decreased risk was also observed when an overall estimate of the pooled analysis and the three cohorts of the current analysis, which were not included in the Pooling Project, was calculated (RR=0.92; 95% CI 0.86–0.98). In accordance with our analyses, the pooled data showed inverse associations for colon cancer risk and total intakes of vitamin A (RR=0.88; 95% CI 0.76–1.02), total vitamin C (RR=0.81; 95% CI 0.71–0.92), and total vitamin E (RR=0.78; 95% CI 0.66–0.92). [21] According to another pooled analyses of 13 cohort studies, [22] the association of the highest versus lowest tertile of supplemental intakes of folate on colon cancer risk was 0.90 (95% CI 0.79–1.02), while we found a statistically significant inverse association of folic acid supplement use on colorectal cancer risk (RR=0.88; 95% CI 0.78–0.98). A pooled analysis of 10 cohort studies reported an inverse association for colorectal cancer risk and the highest versus the lowest quintile of intake for total calcium (RR=0.78; 95% CI 0.69–0.88), which corresponds to our results. [23] Nevertheless, most of the pooled analyses are based on total intakes from dietary and supplemental sources together, and not from supplemental intakes only.

Multivitamin supplements are the most commonly used dietary supplements worldwide, [68] but their role on colorectal cancer is still unclear. Our statistically significant results for multivitamin use and colorectal cancer risk (RR=0.92; 95% CI 0.87–0.97) were very similar

in magnitude to the Physicians' Health Study II Randomized Controlled Trial (PHS II trial; HR=0.89; 95% CI 0.68–1.17). [69] However, colorectal cancer was not the primary outcome in that trial, and its power may have been too low to detect a significant effect of multivitamin supplement use on colorectal cancer. Residual confounding of lifestyle factors, including social economic status, could be a major weakness in our analyses, whereas the PHS II trial had the possibility to adjust for these factors. Furthermore, the intake, dosage and composition of multivitamins can vary substantially between individuals in cohort studies, as the variety of commercially available multivitamin supplements is enormous; in the PHS II trial, multivitamin use was clearly defined and participants were sent fixed calendar packages containing a multivitamin every month. In addition, multivitamins contain several single vitamins and minerals that have potential chemopreventive roles, and are hypothesized to reduce colorectal cancer risk. [70,71] However, it is difficult to identify any single mechanism through which the multiple components in multivitamin supplements could have reduced colorectal cancer risk. It could be that a single mechanism becomes visible in a combination of vitamins and minerals in multivitamins, or that several components in multivitamin supplements reinforce each other. Finally, most of the studies reported on multivitamin use in general. [28-30,57,59] However, the composition of the multivitamins in those studies is unclear as the authors did not further specify whether the supplements contained vitamins only, or also included minerals. The study of Park et al. described that their questionnaire included questions about the use of multivitamins (with or without minerals), [56] but in their analyses it was not clear which type of multivitamins, i.e. with or without minerals, they had studied. In addition, Sanjoaquin et al. reported on use of vitamin supplements in general without any further specification. [58] We therefore assumed that the analyses of Park et al. and Sanjoaquin et al. were based on multivitamin use in general, and we included those studies in our 'use-no use' meta-analyses. It is important to further investigate a potential beneficial role of multivitamin supplement use in the prevention of colorectal cancer and possible underlying mechanisms, taking lifestyle factors into account, and to provide clear descriptions about the composition of multivitamins.

Use of calcium supplements was inversely associated with colorectal cancer risk. A meta-analyses of randomized controlled trials with colorectal cancer as a secondary outcome also suggested that supplemental calcium was inversely, however not statistically significantly associated with colorectal cancer risk in populations with no increased baseline risk (RR=0.62; 95% CI 0.11–3.40). [8] In addition, trials that focused on precursors of colorectal cancer, [8] showed that use of calcium supplements was inversely associated with colorectal

adenoma recurrence (RR=0.82; 95% CI 0.69–0.98), although the inverse association for recurrence of advanced adenomas was not statistically significant (RR=0.77; 95% CI 0.50–1.17). Calcium as a micronutrient can act on many cellular functions, including direct growth-restraining and differentiation- and apoptosis-inducing action on normal and tumor colorectal cells. [72] Based on the generally consistent data from trials and prospective cohort studies and the plausible mechanisms of calcium, we believe that use of calcium supplements might be beneficial in colorectal cancer prevention.

Certain potential limitations of this review warrant consideration. We had limited statistical power in most of the analyses to perform stratified analyses, and thus to assess whether gender, cancer site and geographical region may have been sources of unexplained heterogeneity.

Next, correct assessment of dietary supplement intake is challenging, [73] as errors in measurement of exposure may lead to biased results in several ways. First, recall bias of supplement use by subjects of dose per day could have influenced our results. Second, most studies failed to account for duration of supplement use. For instance, in the Health Professionals Follow-Up study and the Nurses' Health Study dietary supplement use was defined as 'current use during the past year', [63] while in the Womens' Health Study use was described as 'use of any supplement at least once a week'. [59] Given that colorectal cancer has a long induction and latent period, it should have been appropriate if studies accounted for days per week the supplement was taken, and for years of supplement use. Third, there may have been nondifferential misclassification of supplement use in the individual studies. Use of dietary supplements might depend on the season: supplement users may take more dietary supplements during the winter months compared to the summer months. In cohort studies included in this review, seasonal variation was not taken into account. Fourth, the description of type and use of dietary supplements was not always clearly defined, which makes it difficult to compare exposures of different studies. For example, it was unclear what was meant by a multivitamin supplement as no consistent definition exists. The composition of different multivitamin supplements varies, and the composition itself could have changed over time. Further research should focus on a better assessment of dietary supplement use in which accuracy of recall of supplement use, duration of supplement use, and seasonal influences are taken into account, and in which the type of supplement, and the definition of supplement use are clearly stated.

Residual confounding could partly explain the results. Various lifestyle factors are associated with dietary supplement use. Users are more likely to be women, who are higher educated and adopt a healthy lifestyle. [74,75] Adjustments for lifestyle factors differed among the cohort studies, and in some studies adjustments were restricted to age only. [35,51,57] In addition, most of the studies did not adjust for social economic status, or educational level. Still, in many studies, adjustments were made for the most commonly known confounders, such as age, family history of colorectal cancer, body mass index, physical activity, NSAIDs, smoking status, alcohol consumption, energy intake, and dietary factors.

Last, our results could have been affected by small study effects, such as publication bias. Several studies reported risk estimates for selected vitamin supplements and not for all vitamin supplements, and it is not known whether this was due to a very low prevalence of intake, limited statistical power, or for any other reason. In addition, some studies that are included in the Pooling Project, [21] such as the New York State Cohort and the New York University Women's Health Study, are missing in the current meta-analysis, because only published data were included in our analyses. However, Egger's test did not show evidence of small study effects in our analyses, and limited data made it difficult to judge the funnel plots.

The main strength is that this is the first systematic literature review and meta-analyses that focused solely on supplemental intakes and colorectal cancer risk. Pooled analyses investigated dietary and total intakes of vitamins and minerals, but not from supplements specifically. [21-23] In addition, the prospective design of our included studies ruled out potential recall bias. Furthermore, we were able to perform dose-response meta-analyses for several dietary supplements. Finally, the comprehensive literature search, data selection, and data extraction, being performed by five independent reviewers, made the potential of any missed published data unlikely.

In conclusion, this systematic literature review with meta-analyses of prospective cohort studies suggests a potentially beneficial role for use of multivitamins and calcium supplements in colorectal cancer risk. As assessment of dietary supplement use varied widely between studies, and residual confounding may be a major limitation, these findings require confirmation in dedicated cohort studies, such as the VITAL study, [67] that have detailed information on supplemental intakes and colorectal cancer risk. Ideally, findings should be further substantiated by randomized controlled trials, although such trials will require large study populations and a long follow-up time for a sufficient number of

colorectal cancer cases. Since dietary supplement use is ubiquitous in the Western world where colorectal cancer is prevalent, studies on the role of dietary supplement use are of great public health importance and should be a priority.

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SUPPLEMENTAL MATERIAL 2.1 SEARCH STRATEGY

Pubmed

#1 supplement*

#2 Nutraceutical*[tiab] OR Neutraceutical*[tiab]

#3 #1 OR #2

#4 Complementary Therapies[Mesh:NoExp] OR Homeopathy[Mesh:NoExp]

#5 alternative medicine[tiab] OR complementary medicine[tiab] OR alternative therap*[tiab] OR complementary therap*[tiab] OR Homeopathy[tiab]

#6 #4 OR #5

#7 Colorectal neoplasms [MeSH] OR intestinal polyps [MeSH] OR adenomatous polyps [MeSH]

#8 benign*[tiab] OR malign* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR cancer* [tiab] OR tumor [tiab] OR tumors [tiab] OR tumorous[tiab] OR tumour* [tiab] OR adenom*[tiab]

#9 colon [tiab] OR rectum [tiab] OR rectal [tiab] OR colorectum [tiab] OR colorectal [tiab] OR large bowel [tiab] OR large intestine* [tiab] OR gut [tiab] OR colonic [tiab]

#10 #7 OR (#8 AND #9)

#11 (#3 OR #6) AND #10

Embase

#1 supplement*

#2 Nutraceutical*:ti,ab OR Neutraceutical*:ti,ab

#3 #1 OR #2

#4 '*Complementary Therapies*'/de OR *Homeopathy*/de

#5 'alternative medicine':ti,ab OR 'complementary medicine':ti,ab OR 'alternative therapy':ti,ab OR 'alternative therapies':ti,ab OR 'complementary therapy':ti,ab OR 'complementary therapies':ti,ab OR Homeopathy:ti,ab

#6 #4 OR #5

#7 '*Colorectal neoplasms*'/exp OR '*intestinal polyps*'/exp OR '*adenomatous polyps*'/exp

#8 benign*:ti,ab OR malign*:ti,ab OR neoplasm*:ti,ab OR carcinoma*:ti,ab OR cancer*:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumorous:ti,ab OR tumour*:ti,ab OR adenom*:ti,ab

#9 colon:ti,ab OR rectum:ti,ab OR rectal:ti,ab OR colorectum:ti,ab OR colorectal:ti,ab OR 'large bowel':ti,ab OR 'large intestine':ti,ab OR 'large intestines':ti,ab OR gut:ti,ab OR colonic:ti,ab
#10 #7 OR (#8 AND #9)
#11 (#3 OR #6) AND #10

Cochrane

#1 supplement*:ti,ab,kw
#2 (Nutraceutical* OR Neutraceutical*):ti,ab
#3 #1 OR #2
#4 MeSH descriptor Complementary Therapies, this term only
#5 MeSH descriptor Homeopathy, this term only
#6 ("alternative medicine" OR "complementary medicine" OR "alternative therapy" OR "complementary therapy" OR Homeopathy):ti,ab
#7 #4 OR #5 OR #6
#8 MeSH descriptor Colorectal Neoplasms explode all trees
#9 MeSH descriptor Intestinal Polyps explode all trees
#10 MeSH descriptor Adenomatous Polyps explode all trees
#11 #8 OR #9 OR #10
#12 (benign* OR malign* OR neoplasm* OR carcinoma* OR cancer* OR tumor OR tumors OR tumorous OR tumour* OR adenom*):ti,ab
#13 (colon OR rectum OR rectal OR colorectum OR colorectal OR "large bowel" OR "large intestine" OR gut OR colonic):ti,ab
#14 #11 OR (#12 AND #13)
#15 (#3 OR #7) AND #14

Supplementary Table 2.1 Prevalence, ranges of doses, and exposure categories of publications on dietary supplement use and colorectal cancer risk included in the meta-analyses

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
Zhang et al., 2006 [1]	Multivitamins	57% (past use) 29% (current use)	Not applicable	Never use Past use Current use
Jacobs et al., 2003 [2]	Multivitamins	9% (occasional use) 19% (regular use)	Not applicable	No use Occasional use Regular use
Neuhouser et al., 2009 [3]	Multivitamins	41.5%	Not applicable	No Yes
Sanjoaquin et al., 2004 [4]	Multivitamins	27.4%	Not applicable	No use Use
McCarl et al., 2006 [5]	Multivitamins	29.2%	Not applicable	No Yes
Park et al., 2011 [6]	Multivitamins	42.0% (men) 49.0% (women)	Not applicable	No use Use
Lee et al., 2011 [7]	Multivitamins	18.8% (past use) 22.0% (current use 1–5 y) 7.6% (current use 6–9 y) 8.9% (current use 10–15 y) 3.2% (current use 16–19 y) 5.4% (current use ≥20 y)	Not applicable	Never use Current use 1–5 y Current use 6–9 y Current use 10–15 y Current use 16–19 y Current use ≥20 y

Supplementary Table 2.1 continues on next page

Supplementary Table 2.1 *Continued*

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
	Folic acid	82% in NHS* 68% in HPFS*	NHS*: Mean intake (mcg/d): - Past use 158 (in 1980) 146 (in 1984) 157 (in 1986) 169 (in 1990) 197 (in 1994) 358 (in 1998) - Recent use 469 (in 2002) HPFS*: Mean intake (mcg/d): - Past use 193 (in 1986) 202 (in 1990) 230 (in 1994) 386 (in 1998) - Recent use 503 (in 2002)	<50 mcg/d 50–<100 mcg/d 100–<200 mcg/d 200–<400 mcg/d ≥400 mcg/d <50 mcg/d 50–<100 mcg/d 100–<200 mcg/d 200–<400 mcg/d ≥400 mcg/d
Shibata et al., 1992 [8]	Vitamin A Vitamin C	41% (men) 46% (women) 57% (men) 64% (women)	Median daily dose: 10,000 IU/d Median daily dose: 500 mg/d	No Yes (10,000 IU/d) No Yes (500 mg/d)

Supplementary Table 2.1 continues on next page

Supplementary Table 2.1 *Continued*

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
	Vitamin E	49% (men) 54% (women)	Median daily dose: 200 IU/d	No Yes (200 IU/d)
Sellers et al., 1998 [9]	Vitamin A	21%	Mean level of intake: 2,350 IU/d	0 ≤5,000 IU/d >5,000 IU/d
	Vitamin C	28%	Mean level of intake: 145 mg/d	0 ≤180 mg/d >180 mg/d
	Vitamin E	22%	Mean level of intake: 58.3 mg/d	0 ≤30 mg/d >30 mg/d
	Vitamin D	21%	Mean level of intake: 157.9 IU/d	0 ≤400 IU/d >400 IU/d
	Calcium	28%	Mean level of intake: 291.8 mg/d	0 ≤500 mg/d >500 mg/d
Roswall et al., 2010 [10]	Vitamin C	48.8%	5–95% percentile: 7.1–583.2 mg/d	0 ≤39.96 mg >39.96–≤60.00 mg >60.00 mg
	Vitamin E	42.2%	5–95% percentile: 1.2–84.9 mg/d	0 ≤6.66 mg >6.66-–≤10 mg >10 mg

Supplementary Table 2.1 continues on next page

Supplementary Table 2.1 *Continued*

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
	Folic acid	37.6% (CC) ¥ 31.4% (RC) ¥	5–95% percentile:	0
			16.7–364.2 mcg/d	>0–≤83.2 mcg >83.2–≤142.8 mcg >142.8 mcg
Wu et al., 2002 [11]	Vitamin E	13.2% (NHS*)	Not further specified	Never use ≤250 IU 300–500 IU ≥600 IU
		18.3% (HPFS*)	Not further specified	Never use ≤250 IU 300–500 IU ≥600 IU
Lin et al., 2005 [12]	Vitamin D	32%	Not further specified	0 >0–400 IU/d
	Calcium	41%	Not further specified	0 >0–499 mg/d ≥500 mg/d
Martinez et al., 1996 [13]	Vitamin D	Not further specified	Not further specified	No use Use
Kearney et al., 1996 [14]	Vitamin D	33.5%	Not further specified	<4.0 IU/d 4.0–86 IU/d 87–342 IU/d

Supplementary Table 2.1 continues on next page

Supplementary Table 2.1 *Continued*

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
				343–447 IU/d ≥448 IU/d
Park et al., 2007 [15]	Vitamin D	32.6% (men) 38.4% (women)	Not further specified	0 1–≤400 IU/d >400 IU/d
	Calcium	9% (men) 27% (women)	Not further specified	0 1–<200 mg/d ≥200 mg/d
Jarvinen et al., 2001 [16]	Vitamin D	2.4%	Not further specified	No use Use
Flood et al., 2005 [17]	Calcium	43.8%	0–1,130 mg/d	0 0–400 mg/d 401–800 mg/d >800 mg/d
Park et al., 2009 [18]	Calcium	14% (men) 41% (women)	Not further specified	0 >0–<400 mg/d 400–<1,000 mg/d ≥1,000 mg/d
McCullough et al., 2003 [19]	Calcium	9% (men) 34% (women)	Median intake: Tertile 2: 130 mg/d Tertile 3: 730 mg/d	0 1–499 mg/d ≥500 mg/d
Kampman et al., 1994 [20]	Calcium	Not further specified, except:	Not further specified	No use

Supplementary Table 2.1 continues on next page

Supplementary Table 2.1 *Continued*

Author	Supplement	Prevalence of use	Ranges of doses	Exposure categories
		2.2% (in lowest quintile of calcium intake (546 mg/d)) 4.8% (in highest quintile of calcium intake (1,344 mg/d))		Use
Wu et al., 2002 [21]	Calcium	41% (women) 14% (men)	Not further specified	Never use Current use
Stevens et al., 2011 [22]	Folic acid from fortification and supplementation	Not further specified, except: Individual folic acid supplements: 2% (men) 2.1% (women)	Median intakes: From 71 (lowest quintile) to 660 mcg/d (highest quintile)	<101 mcg/d 101–<182 mcg/d 182–<452 mcg/d 452–<560 mcg/d ≥560 mcg/d
Satia et al., 2009 [23]	Garlic	16.4%	Not applicable	No use Any use over the previous 10 years
Dorant et al., 1996 [24]	Garlic	Men: 6.4% (colon) 7.1% (rectum) Women: 3.9% (colon) 3.1% (rectum)	Not applicable	No use Use

¥ CC refers to colon cancer cases; RC refers to rectal cancer cases.

* NHS=Nurses' Health Study; HPFS= Health Professionals Follow-up Study.

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Chapter 3

Dietary supplement use is not associated with recurrence of colorectal adenomas: a prospective cohort study

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ABSTRACT

Background Diet and lifestyle influence colorectal adenoma recurrence. The role of dietary supplement use in colorectal adenoma recurrence remains controversial. In this prospective cohort study, we examined the association between dietary supplement use, total colorectal adenoma recurrence and advanced adenoma recurrence.

Methods and materials Colorectal adenoma cases (n=565) from a former case-control study, recruited between 1995 and 2002 were prospectively followed until 2008. Adenomas with a diameter of ≥1 cm and/or (tubulo)villous histology and/or with high grade dysplasia and/or ≥3 adenomas detected at the same colonic examination were considered advanced adenomas. Hazard ratios and 95% confidence intervals for dietary supplement users (use of any supplement during the past year) compared to nonusers and colorectal adenoma recurrence were calculated using stratified Cox proportional hazard models for counting processes, and were adjusted for age, sex, educational level, and number of colonoscopies during follow up. Robust sandwich covariance estimation was used to adjust for the within subject correlation.

Results A number of 165 out of 565 adenoma patients had at least one colorectal adenoma recurrence during a median person time of 5.4 years and of these, 37 patients had at least one advanced adenoma. One third of the total study population (n=203) used a dietary supplement. Compared to no use, dietary supplement use was not statistically significantly associated with total colorectal adenoma recurrence (HR=1.03; 95% CI 0.79–1.34), nor with recurrent advanced adenomas (HR=1.59; 95% CI 0.88–2.87).

Conclusion This prospective cohort study did not suggest an association between dietary supplement use and colorectal adenoma recurrence.

INTRODUCTION

Dietary supplement use is rising in the Western world. [1] More than half of the American population uses dietary supplements, [1] and in Europe a wide variation in use is present. [2] Supplement use appears to be higher among women, [1] more educated people, [1,3] and people with a healthier lifestyle. [3] Despite limited scientific support for the efficacy of dietary supplements, frequent supplement users take dietary supplements as they believe it may be beneficial in the treatment of acute or chronic illnesses [4] or for the prevention or recurrence of a serious disease, such as cancer. [1]

Colorectal cancer is one of the most common types of cancer in the Western world. [5] It is often proceeded by colorectal adenomas, [6] a precancerous and generally asymptomatic condition. [7] Individuals with multiple and recurrent colorectal adenomas are at higher risk for colorectal cancer. [8] Approximately 15–40% of post polypectomy patients will develop recurrent colorectal adenomas within three years. [9,10] A history of colorectal adenomas, [9] a higher number of prior colorectal adenomas, [9] a family history of colorectal cancer, [11] multiple adenomas at the same colonic examination, [10] an adenoma size of 10 mm or larger, [8,12] and having adenomas with villous features or high-grade dysplasia, [12] are positively associated with colorectal adenoma recurrence.

As dietary supplement use increases in countries where colorectal cancer is prevalent, [5] it is important to provide recommendations for use among those with a high risk of colorectal cancer, i.e. those with recurrent colorectal adenomas. Dietary supplement use in relation to occurrence of a first colorectal adenoma has been extensively studied, [13-17] while the role of dietary supplement use in recurrence of colorectal adenomas has been studied less comprehensively. [18-23] For specific supplements, there is substantial evidence to support or refute a role in colorectal adenoma recurrence: meta-analyses showed that use of calcium supplements significantly reduced the risk of recurrent adenomas, [24] while no protection was observed for use of folic acid supplements against recurrence of colorectal adenomas.[25] Despite the fact that multivitamins are abundantly used, [26] no prospective studies on the association of multivitamin use and colorectal adenoma recurrence have been published. One case control study showed an inverse association between use of multivitamin supplements and colorectal adenoma recurrence, [27] but no marked association was found in another case control study. [28]

We examined the association between the most frequently used dietary supplements, including multivitamin use, and colorectal adenoma recurrence by conducting a prospective cohort study among those with a history of colorectal adenomas in the Netherlands. Moreover, we investigated whether the association differed for colorectal adenomas with advanced pathology.

METHODS AND MATERIALS

Study population

This prospective cohort study originates from an endoscopy-based case-control study on risk factors for colorectal adenomas. In the original case-control study, participants were recruited among those undergoing endoscopy of the large bowel in ten outpatient clinics in the Netherlands between June 1997 and June 2002. Further details about the original case-control study have been described elsewhere. [29]

Colorectal adenoma patients were prospectively followed in the current study. All patients had at least one histologically confirmed colorectal adenoma ever in their life, and were Dutch speaking, of European origin, aged 18 to 75 years at time of the recruitment endoscopy, were not suspected to have hereditary colorectal cancer syndromes (i.e. Lynch Syndrome, familial adenomatous polyposis coli, Gardner's syndrome), did not suffer from inflammatory bowel disease, and did not have a history of colorectal cancer or (partial) bowel resection. Of the 768 colorectal adenoma patients in the original case-control study, 143 adenoma patients were not included into the current study because they did not have endoscopies during follow up. Furthermore, we were not able to retrieve medical information of 50 colorectal adenoma patients. Seven patients had to be excluded due to surgery for colorectal neoplasms detected at recruitment, and three patients became ineligible due to having a histological unconfirmed adenoma only, being diagnosed with proctitis ulcerosa, or being entered twice into the study. Overall, 565 colorectal adenoma patients were included in this study and were prospectively followed. All participants gave informed consent. The Medical Ethics Committee of Radboud University Nijmegen Medical Centre in the Netherlands approved the study.

Assessment of diet, dietary supplement use, and lifestyle factors

Upon recruitment, patients filled out a standardized and validated semi-quantitative food frequency questionnaire to report their habitual dietary intake and dietary supplement use in the year previous to their last endoscopy or bowel complaints. [30,31] Participants were asked to indicate their use of dietary supplements in general, and to report use and frequency of intake (per day, per week, per month or per year) of multivitamins, B-vitamins, vitamin A, vitamin C, vitamin E, vitamin D, calcium, iron, and garlic supplements. Dosage was only asked for use of vitamin C and vitamin E supplements. Participants were classified as users of dietary supplements if they reported to take any dietary supplement during the past year. When patients took no dietary supplements at all during the past year, they were considered as nonusers. General lifestyle information was collected through a lifestyle questionnaire containing questions about age, sex, weight, height, smoking habits, medication use, physical activity, family history of colorectal cancer, and medical history.

Colorectal adenoma recurrence

Information on medical history and recurrence of colorectal adenomas was gathered via medical records from hospital registries just after recruitment and between 2007 and 2009. From each colonic examination, data on adenoma type (villous, tubulovillous, tubular, serrated), adenoma size (mm), adenoma location (caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid, rectum or overlapping location in the bowel) and the number of excised polyps was collected. Any histological confirmed colorectal adenoma detected at least one year after the last positive endoscopy was counted as a recurrent adenoma. In general, endoscopies performed within a year after the last positive endoscopy are mainly done to ascertain if the removal of the adenoma was adequate, rather than to check for recurrences. [32] We assumed that recurrent adenomas, detected within a year after the recruitment endoscopy, were missed during the previous endoscopy. Advanced adenomas were those with a diameter of ≥1 cm and/or villous or tubulovillous histology and/or with high grade dysplasia and/or ≥3 adenomas detected at the same colonic examination. [8] The pathological features of the largest and/or most advanced adenoma were used to characterize the adenomas when there were multiple adenomas at the same colonic examination. If no information about the size, histology, and dysplasia could be retrieved from the endoscopy and/or pathology reports, we assumed that an adenoma was not advanced.

Statistical analysis

Descriptive data (means ± SD, medians and IQR, or percentages) were calculated for the total study population, for patients with adenoma recurrence, and for patients with at least one recurrent adenoma with advanced pathology. In addition, demographic and lifestyle characteristics for dietary supplement users and nonusers were computed.

Stratified cox proportional hazard models for counting processes [33,34] were used to examine the association of dietary supplement use with total colorectal adenoma recurrence, and for the subgroup of recurrent advanced adenomas. Both analyses were compared to the total study population. The conditional approach of the stratified cox proportional hazard model focuses on survival time between recurrent events, which is in this case colorectal adenomas. In this approach, the survival time between two events always starts at 0 for the earlier event, and stops at the later event. [33] In this case, the time until the first event does not influence the composition of the risk set for a second or a later event. [33] The robust sandwich covariance estimation technique was used to adjust for the within subject correlation, if one person had more than one recurrent adenoma. [33] Hazard ratios (HR) were reported with 95% confidence intervals (95% CI). The Cox proportional hazard models were tested for and met the assumption of proportionality; this was done by visually inspecting whether the distance between the log(-log) survival curves was approximately constant. Follow-up time started at the recruitment endoscopy, and ended at the date of the last endoscopy during follow-up. Patients were censored at the date of the last known colonic examination, at the date of diagnosis of colorectal cancer, or at the date of death. Patients who deceased with unknown date of death and patients who reached the end of the follow-up period without a colorectal adenoma recurrence were censored at the date of their last endoscopy.

Covariates were considered as confounders if they correlated with both dietary supplement use and colorectal adenoma recurrence, and if they changed the hazard ratio by 10% or more using backward elimination of variables. We evaluated the following factors as potential confounders: age (years), sex, educational level (low, middle, high), smoking status (current, former, never), alcohol intake (g/day), physical activity (low, medium, high), use of NSAIDs (<1 times/month, ≥1 times/month), family history of colorectal cancer (yes/no), history of adenomas preceding the recruitment endoscopy (yes/no), number of colonoscopies during follow up (1, 2, ≥3), total energy intake (kJ/day), total fibre intake (g/day), total vegetables intake (g/day), total fruit intake (g/day), and total red meat intake (g/

day). In the basic model, we adjusted for age and sex. The fully adjusted model included age, sex, educational level, and number of colonoscopies during follow-up.

Predefined stratified analyses were performed for sex. To assess possible effect measure modification of the association between dietary supplement use and colorectal adenoma recurrence by smoking status and by total fruit and vegetables intake, we stratified our analysis for smoking status (never, former, current) and quartiles of total fruit and vegetables intake (<185, 185–276, 276–385, ≥385 g/day). HR stratified for smoking status were estimated with nonusers, who never smoked, as reference group. In addition, nonusers, who had a relatively low intake of fruit and vegetables of <185 g/day, were defined as reference group to evaluate HR stratified for total fruit and vegetables intake. The P-value for interaction was calculated by the Chi-square test of the likelihood ratio test, comparing the models for nonusers and users by smoking status and by total fruit and vegetables intake.

In our cohort, all participants (n=565) had an endoscopy at recruitment. However, part of the cohort did not have a colorectal adenoma at the recruitment endoscopy, but were diagnosed with an adenoma before recruitment. Therefore, a sensitivity analysis was performed in which the cohort was restricted to those persons (n=406) who had a colorectal adenoma at the recruitment endoscopy. Furthermore, three other sensitivity analyses were done, one for persons who had a history of adenomas preceding the recruitment endoscopy compared to persons who did not have a history of adenomas before recruitment, an analysis restricted to those persons without a family history of colorectal cancer (n=424), and an analysis in which nonusers were defined as taking <4 dietary supplements per month instead of no dietary supplement at all. A level of significance of less than .05 was considered statistically significant. The statistical software program SAS 9.2 (SAS Inc, Cary, USA, 2004) was used for statistical analysis.

RESULTS

Characteristics of the study population are shown in **Table 3.1**. The mean (± SD) age at recruitment of the total study population (n=565) was 58.8 (± 9.7) years and the median person time was 5.4 (P25–P75=3.7–7.0) years. About one third of the total study population (n=203) used a dietary supplement, and about two third (n=344) had advanced colorectal adenomas at the recruitment endoscopy. A number of 165 out of 565 patients (29%) had

Table 3.1 General characteristics for the total population, for cases with total colorectal adenoma recurrence, and for cases with at least one adenoma recurrence with advanced pathology in a prospective cohort study of 565 adenoma patients

		Colorectal adenoma recurrence	
	Total population (n=565)	Total (n=165)	Advanced pathology¥ (n=37)
Person time [y, median (P25–P75)]	5.4 (3.7–7.0)	6.3 (4.7–7.6)	6.7 (5.6–8.1)
Demographic characteristics			
Age [years, mean ± SD]	58.8 ± 9.7	59.4 ± 9.7	59.7 ± 11.3
Women [n (%)]	270 (47.8)	71 (43.0)	16 (43.2)
Education [n (%)]*			
Low	177 (31.1)	52 (31.5)	17 (46.0)
Medium	208 (36.8)	61 (37.0)	10 (27.0)
High	129 (22.8)	37 (22.4)	6 (16.2)
Lifestyle characteristics			
BMI [kg/m^2, mean ± SD]	26.2 ± 3.8	26.2 ± 3.4	26.4 ± 3.7
Smokers [n (%)]			
Never	195 (34.5)	55 (33.3)	12 (32.4)
Former	223 (39.5)	65 (39.4)	16 (43.2)
Current	147 (26.0)	45 (27.3)	9 (24.3)
NSAID use [≥1x/month, n (%)]	148 (26.2)	44 (26.7)	6 (16.2)
Physical activity [n, (%)]			
Low	208 (36.8)	62 (37.6)	13 (35.2)
Medium	179 (31.7)	53 (32.1)	14 (37.8)
High	178 (31.5)	50 (30.3)	10 (27.0)
Medical characteristics			
Family history of CRC [n (%)]	141 (25.0)	45 (27.3)	10 (27.0)
Adenoma pathology at recruitment [n (%)]			
Non advanced	221 (39.1)	61 (37.0)	10 (27.0)
Advanced¥	344 (60.9)	104 (63.0)	27 (73.0)
Former adenomas before recruitment endoscopy [n (%)]			
1	172 (30.5)	54 (32.9)	13 (35.1)
2	41 (7.3)	16 (9.8)	4 (10.8)
≥3	19 (3.4)	10 (6.1)	4 (10.8)
Number of colorectal adenoma recurrence(s) during follow-up [n (%)]§			
1	108 (19.1)	108 (65.5)	13 (35.1)
2	40 (7.1)	40 (24.2)	13 (35.1)
≥3	17 (3.0)	17 (10.3)	11 (29.7)
No. of colonoscopies [n (%)]			
1	320 (56.6)	110 (66.7)	27 (73.0)
2	169 (29.9)	41 (24.9)	7 (18.9)
≥3	76 (13.5)	14 (8.5)	3 (8.1)

Table 3.1 continues on next page

Table 3.1 *Continued*

	Total population (n=565)	Colorectal adenoma recurrence	
		Total (n=165)	Advanced pathology[¥] (n=37)
Dietary supplement use[¶]			
Any [n (%)]	203 (35.9)	64 (38.8)	16 (43.2)
Multivitamins [n (%)]	99 (17.5)	28 (17.0)	6 (16.2)
Vitamin C [n (%)]	91 (16.1)	32 (19.4)	9 (24.3)
Vitamin B complex [n (%)][#]	36 (6.4)	13 (7.9)	4 (10.8)
Calcium + vitamin D [n (%)]	34 (6.0)	10 (6.1)	3 (8.1)
Vitamin E [n (%)]	25 (4.4)	7 (4.2)	0
Dietary intake			
Total energy intake [kJ/day, mean ±SD]	8,756 ± 2,492	8,748 ± 2,550	9,092 ± 2,983
Vegetables intake [g/day, median (IQR)]	113.6 (90.2–140.7)	111.5 (85.5–142.0)	116.6 (100.0–160.2)
Fruit intake [g/day, median (IQR)]	130.0 (74.8–247.9)	126.4 (71.8–243.3)	142.2 (71.1–245.4)
Red meat intake [(g/day, median (IQR)]	58.8 (32.6–80.7)	62.5 (37.6–82.1)	70.6 (54.1–88.9)
Alcohol intake [g/day]	15.3 ± 18.7	15.6 ± 19.0	14.4 ± 17.6

[¥] Advanced adenomas are those with a diameter of ≥1 cm, and/or (tubulo)villous histology, and/or with high grade dysplasia, and/or ≥3 adenomas detected at the same colonic examination.
[*] <10% is missing.
[§] Number of adenoma recurrences during follow up starting from the recruitment endoscopy.
[¶] Use of any dietary supplement during the past year.
[#] Includes folate.

one or multiple colorectal adenoma recurrences during follow-up. Compared to the total population, patients with a colorectal adenoma recurrence used slightly more dietary supplements, were more often men, were slightly older, and had more often former adenomas. Recurrent adenomas showed advanced pathology in 37 (22%) out of the 165 patients with a colorectal adenoma recurrence, and of these 27 (73%) already had an advanced adenoma at recruitment endoscopy. Patients who had an advanced adenoma recurrence used more dietary supplements, were slightly older, were lower educated, used less NSAIDs, and had more often a history of adenomas preceding the recruitment endoscopy compared to both the total study population and patients with total colorectal adenoma recurrence.

Table 3.2 shows general characteristics of dietary supplement users and nonusers. Of the 203 dietary supplement users, 66 (32.5%) users experienced a recurrent colorectal adenoma, and 16 (7.9%) users had a least one recurrent adenoma with advanced pathology. Among the nonusers (n=362), 99 (26.5%) had an adenoma recurrence, and 21 (5.8%) experienced at least one recurrent advanced adenoma. Compared to nonusers, dietary

supplement users were more often women, were higher educated, were more physically active, had a slightly lower body mass index, had more often a family history of colorectal cancer, and consumed more vegetables and fruit.

Dietary supplement use was not associated with total colorectal adenoma recurrence (HR=1.03; 95% CI 0.79–1.34), nor was it statistically significantly associated with recurrent adenomas that showed advanced pathology (HR=1.59; 95% CI 0.88–2.87) after adjustments for age, sex, educational level, and number of colonoscopies during follow up (**Table 3.3**). Use of multivitamin supplements (HR=0.88; 95% CI 0.62–1.24), vitamin C supplements (HR=0.83; 95% CI 0.58–1.17), and calcium (including vitamin D) supplements (HR=0.83; 95% CI 0.45–1.50) did not show an association with total and advanced colorectal adenoma recurrence either. In exploratory analyses, use of B-vitamin supplements was associated with a statistically significantly increased risk of total colorectal adenoma recurrence (HR=1.58; 95% CI 1.05–2.36), but not with recurrent adenomas that showed advanced pathology (HR=1.59, 95% CI 0.59–4.27).

Table 3.2 General characteristics of dietary supplement users versus nonusers in a prospective cohort study of 565 adenoma patients

	Dietary supplement use	
	Users[¥] (n=203)	Nonusers[*] (n=362)
Person time [years, median (P25–P75)]	5.4 (3.8–7.1)	5.4 (3.6–7.0)
Demographic characteristics		
Age [years, mean ± SD]	58.9 ± 9.7	58.9 ± 9.7
Women [n (%)]	119 (58.6)	151 (41.7)
Education [n (%)][$]		
Low	47 (23.2)	130 (35.9)
Medium	82 (40.4)	126 (34.8)
High	56 (27.6)	73 (20.2)
Lifestyle characteristics		
Body Mass Index [kg/m^2, mean ± SD]	25.6 ± 3.7	26.5 ± 3.9
Smokers [n (%)]		
Never	72 (35.5)	123 (34.0)
Former	80 (39.4)	143 (39.5)
Current	51 (25.1)	96 (26.5)
NSAID use [≥1 times/month, n (%)]	54 (25.6)	94 (26.0)
Physical activity [n (%)]		
Low	62 (30.5)	146 (40.3)
Medium	67 (33.0)	112 (30.9)
High	74 (36.5)	104 (28.7)

Table 3.2 continues on next page

Table 3.2 *Continued*

	Dietary supplement use	
	Users[¥] (n=203)	Nonusers[*] (n=362)
Medical characteristics		
Family history of CRC [n (%)]	58 (28.6)	83 (22.9)
Adenoma pathology at recruitment [n (%)]		
Non advanced	89 (43.8)	132 (36.5)
Advanced[¶]	114 (56.2)	230 (63.5)
Number of colorectal adenoma recurrence(s) during follow-up [n (%)][#]		
1	42 (20.7)	66 (18.2)
2	16 (7.9)	24 (6.6)
≥3	8 (3.9)	9 (2.5)
At least one advanced adenoma recurrence(s) during follow-up [n (%)]	16 (7.9)	21 (5.8)
Former adenomas before recruitment endoscopy [n (%)]		
1	57 (28.1)	115 (31.9)
2	17 (8.4)	24 (6.7)
≥3	5 (2.5)	14 (3.9)
No. of colonoscopies [n (%)]		
1	117 (57.6)	203 (56.1)
2	56 (27.6)	113 (31.2)
≥3	30 (14.8)	46 (12.7)
Dietary supplement intake		
Multivitamins [n (%)]	99 (48.8)	-
Vitamin C [n (%)]	91 (44.8)	-
Vitamin B complex [n (%)][^]	36 (17.7)	-
Calcium + vitamin D [n (%)]	34 (16.8)	-
Vitamin E [n (%)]	25 (12.3)	-
Vitamin A/D [n (%)]	9 (4.4)	-
Dietary intake		
Total energy intake [kJ/day, mean ± SD]	8,456 ± 2,542	8,924 ± 2,452
Vegetables intake [g/day, median (P25–P75)]	121.3 (91.4–139.6)	119.8 (89.4–141.0)
Fruit intake [g/day, median (P25–P75)]	199.6 (98.3–252.5)	170.0 (63.0–244.1)
Red meat intake [g/day, median (P25–P75)]	52.9 (28.3–75.2)	61.7 (37.5–83.2)
Alcohol intake [g/day, mean ± SD]	15.1 ± 18.5	15.5 ± 18.8

[¥] Use of any dietary supplement during the past year.
[*] No use of dietary supplements during the past year.
[$] <10% is missing.
[¶] Advanced adenomas are those with a diameter of ≥1 cm, and/or (tubulo)villous histology, and/or with high grade dysplasia, and/or ≥3 adenomas detected at the same colonic examination.
[#] Number of adenoma recurrences during follow up starting from the recruitment endoscopy.
[^] Includes folate.

Associations did not markedly differ between men (HR=1.07; 95% CI 0.72–1.60) and women (HR=0.98; 95% CI 0.69–1.38). No association for colorectal adenoma recurrence and dietary supplement use was shown in the lower and higher quartiles of total fruit and

Table 3.3 Associations of dietary supplement use with total colorectal adenoma recurrence and advanced adenoma recurrence in a cohort of 565 colorectal adenoma cases

	Total adenoma recurrence		Advanced adenoma recurrence[¥]	
Dietary supplement use	No use[*] HR	Use[$] HR (95% CI)	No use[*] HR	Use[$] HR (95% CI)
Any dietary supplement				
No. of cases	101	64	21	16
HR, age & sex adjusted	1.0	1.07 (0.82–1.39)	1.0	1.59 (0.87–2.91)
HR, fully adjusted[¶]	1.0	1.03 (0.79–1.34)	1.0	1.59 (0.88–2.87)
Multivitamins				
No. of cases	137	28	31	6
HR, age & sex adjusted	1.0	0.87 (0.61–1.24)	1.0	1.74 (0.86–3.56)
HR, fully adjusted[¶]	1.0	0.88 (0.62–1.24)	1.0	1.55 (0.74–3.26)
Vitamin C				
No. of cases	133	32	28	9
HR, age & sex adjusted	1.0	0.83 (0.58–1.19)	1.0	0.84 (0.36–1.96)
HR, fully adjusted[¶]	1.0	0.83 (0.58–1.17)	1.0	0.92 (0.39–2.14)
B-vitamins[#]				
No. of cases	152	13	33	4
HR, age & sex adjusted	1.0	1.64 (1.09–2.48)	1.0	1.59 (0.58–4.37)
HR, fully adjusted[¶]	1.0	1.58 (1.05–2.36)	1.0	1.59 (0.59–4.27)[$]
Calcium and vitamin D				
No. of cases	155	10	34	3
HR, age & sex adjusted	1.0	0.86 (0.48–1.52)	1.0	2.25 (0.88–5.75)
HR, fully adjusted[¶]	1.0	0.83 (0.45–1.50)	1.0	2.27 (0.88–5.89)

[¥] Advanced adenomas are those with a diameter of ≥1 cm, and/or (tubulo)villous histology, and/or with high grade dysplasia, and/or ≥3 adenomas detected at the same colonic examination.
[*] No use of dietary supplements during the past year.
[$] Use of any dietary supplement during the past year.
[¶] Hazard ratio with its 95% CI adjusted for age, sex, educational level, number of colonoscopies during follow up.
[#] Includes folate.

vegetables intakes (P for interaction: 0.93). Effect measure modification of smoking status was not present for the association of dietary supplement use and adenoma recurrence: P for interaction was 0.63 (**Table 3.4**).

Sensitivity analyses showed that restricting the cohort to persons who all had an adenoma recurrence at the recruitment endoscopy did not markedly change the association between dietary supplement use and total colorectal adenoma recurrence (HR=1.11; 95% CI 0.84–1.47). In additional sensitivity analyses, no differences in associations for dietary supplement use and total colorectal adenoma recurrence were seen for persons with a history of adenomas preceding the recruitment endoscopy (HR=1.24; 95% CI 0.76–2.02) and

Table 3.4 Hazard ratios for dietary supplement use and total colorectal adenoma recurrence by smoking status and total fruit and vegetables intake in a prospective cohort study of 565 adenoma patients

	Smoking status		
Dietary supplement use	Never	Former	Current
No use[¥]			
No. of cases	29	44	28
HR (95% CI)[$]	1.0	1.04 (0.68–1.59)	1.09 (0.71–1.69)
Use[*]			
No. of cases	26	21	17
HR (95% CI)[$]	1.11 (0.69–1.78)	0.93 (0.60–1.45)	1.25 (0.75–2.08)
P for interaction			0.63

	Total fruit and vegetables intake (g/day)			
Dietary supplement use	<185	185–276	276–385	≥385
No use[¥]				
No. of cases	25	31	23	22
HR (95% CI)[$]	1.0	0.96 (0.63–1.46)	1.15 (0.71–1.87)	0.91 (0.56–1.47)
Use[*]				
No. of cases	20	16	14	14
HR (95% CI)[$]	1.02 (0.63–1.66)	1.18 (0.74–1.89)	0.85 (0.49–1.45)	1.10 (0.61–1.95)
P for interaction				0.93

[¥] No use of dietary supplements during the past year.
[*] Use of any dietary supplement during the past year.
[$] Hazard ratio with its 95% CI adjusted for age, sex, educational level, number of colonoscopies during follow up.

for persons without former adenomas at baseline recruitment (HR=0.94; 95% CI 0.69–1.28). A borderline statistically significant increased risk was found for dietary supplement use and colorectal adenoma recurrence (HR=1.39; 95% CI 1.02–1.89) in persons with no known family history of colorectal cancer. Finally, sensitivity analyses restricted to those who used no or less than 4 dietary supplements per month as the reference category, did not change the association for dietary supplement use and total colorectal adenoma recurrence in our study either (HR=1.13; 95% CI 0.86–1.48).

DISCUSSION

In this prospective cohort study, dietary supplement use was not associated with total colorectal adenoma recurrence, nor with recurrence of adenomas with advanced pathology. The lack of association for colorectal adenoma recurrence also applied to use

of multivitamin supplements, vitamin C supplements, and calcium (including vitamin D) supplements. Exploratory analyses suggested that use of B-vitamin supplements were associated with a statistically significantly increased risk of total adenoma recurrence, but not with recurrence of colorectal adenomas with advanced pathology.

To our knowledge, no other prospective study evaluated the association between multivitamin supplement use and colorectal adenoma recurrence. Our prospective study showed no statistically significant association for use of multivitamin supplements with colorectal adenoma recurrence, which was in line with a case-control study of 198 recurrent adenoma cases and 347 controls who had a history of one or more polyps. [28] Our findings contrast with a second case-control study with 183 recurrent adenoma cases and 265 controls who had a past history of a colonic neoplasm; there they found a decreased risk of adenoma recurrence with multivitamin supplement use. [27] Nevertheless, case-control studies may be subject to recall bias. Prospective cohort designs have been largely perceived as an effective strategy to avoid exposure recall bias, which make prospective studies more reliable to predict associations.

The association between colorectal adenoma occurrence and use of dietary supplements has been extensively evaluated in many epidemiological studies. [13-17] However, less comprehensive results have been reported for colorectal adenoma recurrence. According to a meta-analysis of randomized controlled trials, calcium supplementation statistically significantly reduced the risk of colorectal adenoma recurrence. [24] A prospective observational study within the Wheat Bran Fiber Trial showed no association for use of supplemental vitamin D and colorectal adenoma recurrence, [18] whereas in observational analyses in the Polyp Prevention Trial an inverse association was observed for any use of vitamin D supplements and recurrent adenomas compared to no use. [23] This difference in association could be explained by the fact that participants in the Wheat Bran Fiber trial may have more homogeneous levels of vitamin D due to higher sunlight exposure. [23] There is no other study that investigated the association of supplemental vitamin C, as a single supplement, and total colorectal adenoma recurrence. One small intervention study found a significant reduction in the recurrence of polyps with a combination of a vitamin A, C and E supplement in 70 randomly assigned patients compared to 78 patients who received no treatment. [35] No effects were found in an intervention study among 143 patients randomly assigned to a combined supplement of vitamin C and E or placebo and recurrence of colorectal adenomas, and in another intervention study of 864 randomly assigned patients to four treatment groups. [19,36] Another randomized controlled trial did not

provide evidence for a potential role of vitamin E supplement use in colorectal adenoma recurrence. [19] Due to the low number of users of these specific dietary supplements in our study, it was not possible to show an interpretable association for use of supplemental calcium and vitamin D, vitamin C and vitamin E and colorectal adenoma recurrence.

In this study, use of B-vitamin supplements, including folic acid, was associated with a statistically significantly increased risk of total adenoma recurrence, but not with recurrence of colorectal adenomas that showed advanced pathology. According to randomized controlled trials, supplemental folic acid may not prevent recurrence of colorectal adenomas, [25,37,38] but may instead increase the recurrence of multiple and advanced colorectal adenomas. [39] We were not able to evaluate the role of folic acid supplement use separately because in our food frequency questionnaire supplemental B-vitamin use was measured together as one dietary supplement as those B-vitamin supplements are mostly used. No other study evaluated whether a combination of B-vitamins in one supplement was associated with colorectal adenoma recurrence. However, due to the small number of B-vitamin supplement users in our study we should interpret this possible chance finding with caution.

Generally, diets of dietary supplement users are higher in fruit and vegetables compared with those of nonusers. [40] Randomized controlled trials with diets high in fruit and vegetables did not find significant benefits for higher fruit and vegetables intakes in reducing the risk of adenoma recurrence. [41,42] In our study, we found no association for dietary supplement use and colorectal adenoma recurrence in the lower and higher quartiles of total fruit and vegetables intakes. To our knowledge, no other study investigated whether the association between dietary supplement use and colorectal adenoma recurrence is different for low versus high intakes of fruit and vegetables. As fruit and vegetables are rich sources of micronutrients and bioactive compounds, [43] and a small reduction in risk for colorectal cancer and fruit and vegetables has been observed in large prospective studies, [44,45] it is useful to evaluate whether fruit and vegetables can reduce the risk in patients with recurrent colorectal adenomas.

Several methodological issues concerning dietary supplement use need to be considered. First, comparison of dietary supplement use between different studies is challenging because of different definitions of supplements, and different frequencies of use required for a subject to be defined as user. In our cohort of adenoma cases, supplement use was defined as an intake of any dietary supplement during the past year. In observational

analyses within the Polyp Prevention Trial, participants were defined as user when they used any calcium or vitamin D supplement during any of the time periods used for analysis, and use was categorized in tertiles of intake of supplemental calcium and vitamin D. [23] No other observational studies were done that investigated dietary supplement use and colorectal adenoma recurrence. Moreover, no or infrequent users, who used no or less than 4 dietary supplements per month, may also be representative for subjects who did not use any dietary supplement at all. Yet, sensitivity analyses with subjects who used <4 dietary supplements per month as the reference, did not change the associations in our study. Thus, those no or infrequent users might not differ much from nonusers, who did not take any dietary supplement at all, in this study.

A second issue regarding dietary supplement use we need to consider, is the fact that we were not able to calculate the total nutrient intake by foods and dietary supplements together as information on dosage and duration was not assessed. Observational analyses within two randomized controlled trials showed results for colorectal adenoma recurrence and total intake of micronutrients from supplements and diet together. [18,21,22] The Wheat Bran Fiber Trial and the Polyp Prevention Trial indicated that higher intakes compared to lower intakes of total vitamin B6, [22] total folate, [22] total calcium, [18] and total vitamin A [21] were inversely associated with recurrence of colorectal adenomas, whereas non-significant associations were shown for total vitamin B12. [22] In our study, it would have been preferable if a detailed assessment on dietary supplement use and changes in use was available.

A third issue is that use of dietary supplements can vary throughout the year. Supplement users may take more dietary supplements during the winter months compared to the summer months, whereby confounding by season might bias the results. However, as subjects were recruited for the study throughout the year and supplement use was assessed by asking over the preceding year, adjusting for seasonal influences did not change the associations between dietary supplement use and colorectal adenoma recurrence in our study.

Fourth, in our study we relied on self-reported dietary supplement use, which made misclassification of the exposure possible. However, prior studies have demonstrated such data to be reliable. [46,47] Moreover, dietary supplement use was recorded before any knowledge of colorectal adenoma recurrence, thus reducing the likelihood of reporting biases. Also, participants could have changed their intake of dietary supplements after polypectomy based on their health status and disease risk, [48] but according to Almendingen

et al. there is no existing evidence for meaningful lifestyle changes following the diagnosis of an adenoma. [49] We therefore assume that intake of dietary supplements by colorectal adenoma patients is relatively constant during the follow up period in our study, which makes self-reported dietary supplement use in the year prior to polypectomy a reliable indicator for the actual intake.

The last issue we want to address is the fact that the lack of association between use of any dietary supplement and colorectal adenoma recurrence could be a mere product of a neutralization of individual effects of each nutrient supplement. Unfortunately, we were not able to further explore the association of use of individual dietary supplements and recurrent colorectal adenomas due to the small study size.

Besides the methodological issues regarding dietary supplement use, another limitation of our study is the small sample size, which decreased the power to detect associations. One of the strengths of our study is the long person time of this prospective cohort, which enabled us to detect several recurrent adenoma events. Another strength is that residual confounding will be unlikely in our study, because we acquired extensive dietary, lifestyle, and medical information from the adenoma cases. Consistent with literature, dietary supplement users in our study were more often women, [1] were higher educated, [1,3] had a healthier lifestyle, [1,3] and were less likely to smoke. [50] We were able to adjust for these potential confounders. However, as dietary supplement users probably have a healthier diet and are more health conscious than nonusers, which involves many different factors, residual confounding can never be completely ruled out.

In conclusion, we did not find an indication that use of dietary supplements has a beneficial or harmful role on colorectal adenoma recurrence. In order to make public health policies for prevention of recurrent adenomas and colorectal cancer, future studies with extensive information on habitual dietary supplement use are needed.

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Chapter 4

Dietary supplement use and colorectal adenoma risk in individuals with Lynch syndrome: the GeoLynch cohort study

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ABSTRACT

Background Individuals with Lynch syndrome have a high lifetime risk of developing colorectal tumors. In this prospective cohort study of individuals with Lynch syndrome, we examined associations between use of dietary supplements and occurrence of colorectal adenomas.

Methods and materials Using data of 470 individuals with Lynch syndrome in a prospective cohort study, associations between dietary supplement use and colorectal adenoma risk were evaluated by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) using cox regression models adjusted for age, sex, and number of colonoscopies during person time. Robust sandwich covariance estimation was used to account for dependency within families.

Results Of the 470 mismatch repair gene mutation carriers, 122 (26.0%) developed a colorectal adenoma during an overall median person time of 39.1 months. Forty percent of the study population used a dietary supplement. Use of any dietary supplement was not statistically significantly associated with colorectal adenoma risk (HR=1.18; 95% CI 0.80–1.73). Multivitamin supplement use (HR=1.15; 95% CI 0.72–1.84), vitamin C supplement use (HR=1.57; 95% CI 0.93–2.63), calcium supplement use (HR=0.69; 95% CI 0.25–1.92), and use of supplements containing fish oil (HR=1.60; 95% CI 0.79–3.23) were also not associated with occurrence of colorectal adenomas.

Conclusion This prospective cohort study does not show inverse associations between dietary supplement use and occurrence of colorectal adenomas among individuals with Lynch syndrome. Further research is warranted to determine whether or not dietary supplement use is associated with colorectal adenoma and colorectal cancer risk in MMR gene mutation carriers.

INTRODUCTION

Individuals with Lynch syndrome have pathogenic germline mutations in genes involved in DNA mismatch repair (MMR), i.e. MLH1, MSH2, MSH6, PMS2, [1-5] or in the EPCAM gene. [6,7] Approximately 3% of all colorectal cancers are induced by Lynch syndrome. [8,9] The adenoma-carcinoma sequence seems to be accelerated in MMR gene mutation carriers, [10] and carriers have a 25–70% risk of developing colorectal cancer up to age 70, at a relatively young age, [2-5,11] compared to 2–5% in the general Western population. [12,13]

Removal of colorectal adenomas lowers risk of colorectal carcinomas in individuals with Lynch syndrome. [14,15] Therefore, those persons are generally advised to follow strict periodic endoscopic surveillance to detect colorectal adenomas. [15,16] Considering the high lifetime risk of developing adenomas and carcinomas in MMR gene mutation carriers, [2-5] it is very relevant to study whether modifiable lifestyle factors, including dietary supplement use, can affect this risk. As shown in previous studies from our group, excess body weight, [17] smoking, [18] and a dietary pattern high in snack foods [19] were associated with an increased risk of colorectal adenomas in persons with Lynch syndrome. Retrospective case-control studies in Lynch syndrome suspected families showed that increased fruit consumption and dietary fiber intake possibly decreased the risk of colorectal tumors. [20]

Although a healthy diet provides a sufficient amount of vitamins and minerals, many individuals take vitamin and mineral supplements regularly, hoping to further improve their health and to prevent acute or chronic illnesses and serious diseases, such as cancer. [21,22] Dietary supplement use and colorectal adenoma risk have been extensively investigated in the general population. No convincing evidence for an association between multivitamin supplement use, [23] folic acid supplement use, [24] and antioxidant supplement use and adenoma occurrence was found, [25,26] whereas calcium supplement use might contribute to a lower risk of colorectal adenomas. [27] MMR gene mutation carriers might have a higher use of dietary supplements compared to the general Dutch population based on their health status and risk. [28] Up until now, as far as we know, no studies on dietary supplement use and colorectal adenomas among individuals with Lynch syndrome were conducted.

The objective of this study was to prospectively examine associations between the most frequently used dietary supplements and colorectal adenoma development in a cohort study of individuals with Lynch syndrome.

METHODS AND MATERIALS

Study population

Individuals with Lynch syndrome participated in the GeoLynch cohort study which was described earlier. [17] Briefly, carriers of a germline mutation in at least one of the mismatch repair genes were identified via linkage to a hereditary tumor registration of the Netherlands Foundation for the Detection of Hereditary Tumors in Leiden, the Radboud University Nijmegen Medical Center in Nijmegen, and the University Medical Center Groningen in Groningen, the Netherlands. Participants had to be between 18 and 80 years of age, Dutch-speaking, white, and mentally competent to be eligible for the study. Terminally ill patients, and those with familial adenomatous polyposis, inflammatory bowel diseases, a complete proctocolectomy or colostomy were excluded.

With approval of their medical specialist, a total of 713 mutation carriers were invited to participate in the study between July 2006 and July 2008. Six hundred ninety-five out of 713 people could be contacted of whom nine were ineligible. Of these, 73% (499 of 686) agreed to participate. We were unable to retrieve medical and personal information from 29 participants. Therefore, a total of 470 participants from at least 161 families were included in this study. The Medical Ethics Committee of the Radboud University Nijmegen Medical Center approved the study. All participants gave written informed consent.

Exposure assessment

At recruitment, dietary supplement use was collected using a self-administered questionnaire. Information on dietary supplement use included frequency of intake (no intake in the previous month, once a month, 2–3 days a month, once a week, 2–3 days a week, 4–5 days a week, 6–7 days a week), amount of intake (1, 2, 3, 4, or ≥5 tablets, capsules or droplets), and brand names of supplemental multivitamins, vitamin C, B-vitamins, folic acid, vitamin D (including vitamin A), vitamin E, calcium, iron, and fish oil. In addition, participants could indicate whether they used other supplements that were not covered by the questionnaire. In this study, users of dietary supplements were defined as those taking any dietary supplement during the last month. When patients took no dietary supplements at all during the last month, they were considered nonusers. Habitual dietary intake was collected using a 183-item self-administered and validated food frequency questionnaire. [29,30] General lifestyle information was collected with a lifestyle questionnaire containing

questions about age, sex, weight, height, smoking habits, medication use, physical activity,[31] family history of colorectal cancer, and medical history.

Outcome data

Medical information, including information about medical history and colorectal adenomas and carcinomas, was obtained by reviewing medical records regularly from all subjects via the participating centers until information was complete. From every participant, information about previously performed colonoscopies, colorectal surgery, cancer, and adenomatous polyps was gathered before recruitment and during follow up until December 31, 2010. We ascertained detailed information from pathology reports about location, size, and histology for all documented colorectal adenomas that occurred during follow up.

Data analysis

The outcome of our analysis was the time to diagnosis of the first pathology-confirmed colorectal adenoma. Descriptive statistics were used to describe the demographic characteristics, and characteristics on lifestyle, medical status, dietary supplement use and dietary intake of all 470 MMR gene mutation carriers and from those who were diagnosed with a colorectal adenoma during follow up. In addition, general characteristics were computed for dietary supplement users versus nonusers. Differences in baseline characteristics between users and nonusers were tested by the Mann-Whitney U test (continuous variables) or the Chi-square test (categorical variables).

Cox proportional hazards regression was used to investigate associations of dietary supplement use and colorectal adenoma occurrence. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were reported, and robust sandwich covariance estimation was used to account for dependency of observations within families. The Cox proportional hazard models were tested for and met the assumption of proportionality by visually inspecting whether the distance between the log(-log) survival curves was approximately constant. Person time started at the date of the most recent colonoscopy before assessment of dietary supplement use and ended at the date of colonoscopy of the first diagnosed colorectal adenoma during follow up. Participants without a colorectal adenoma diagnosis or without a detectable colorectal adenoma were censored at the date of their last known colonoscopy during follow up.

The following covariates were evaluated as potentially confounding variables: age (continuous), sex, educational level (categorical: high vs lower educated), number of colonoscopies during person time (continuous), history of colorectal adenomas (yes/no), history of carcinomas (yes/no), physical activity level (categorical: high vs lower physically active), smoking status (current, former, never), body mass index (continuous), regular use of NSAIDs (<1 times/week, ≥1 times/week), alcohol intake (g/d), total energy intake (kJ/d), total vegetables intake (g/d), total fruit intake (g/d), and total red meat intake (g/d). In the basic model, we adjusted for age and sex. Covariates were considered as confounders if they correlated with any use of dietary supplements and colorectal adenoma risk, and if they changed the hazard ratio by ≥10% using forward selection. The maximally adjusted model included age, sex, and number of colonoscopies during person time.

Stratified analyses for the association of dietary supplement use and colorectal adenoma risk were conducted for MMR carriers with a history of colorectal neoplasms before study entry (recurrence), and for those without (first occurrence). To assess possible effect measure modification of associations between dietary supplement use and colorectal adenoma risk, we stratified our analysis for smoking status (never, former, current) and total fruit and vegetables intake (in quartiles: <179, 179–283, 283–387, ≥387 g/day). Nonusers, who never smoked, were defined as reference group to estimate HRs stratified for smoking status. In addition, nonusers who had a relatively low intake of fruit and vegetables of <179 g/day, were defined as reference group to evaluate HRs stratified for total fruit and vegetables intake. To test for multiplicative interaction we used a log likelihood ratio test, comparing models for nonusers and users by smoking status and by strata of total fruit and vegetables intake.

A sensitivity analysis was performed for the association between any use and use of specific types of dietary supplements and colorectal adenoma risk, in which person time started at the time of assessment of dietary supplement use. $P<0.05$ was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

In this cohort of MMR gene mutation carriers, 122 (26.0%) of 470 subjects developed a colorectal adenoma during an overall median person time of 39.1 months (**Table 4.1**). The total person time was 18,449 person months. About 44% of the colorectal adenoma

cases used a dietary supplement versus 40% in the total cohort. Colorectal adenoma cases were slightly older and lower educated compared to the total cohort. In addition, more persons smoked, and alcohol intake was higher in colorectal adenoma cases compared to the total cohort.

Table 4.1 General characteristics of the mismatch repair gene mutation carriers in the GeoLynch cohort study

		Total population (n=470)	Colorectal adenoma cases (n=122)
Person time [months, median (P25–P75)]		39.1 (25.1–49.8)	27.8 (22.4–47.3)
Demographic characteristics			
Age at study entry [years, median (P25–P75)]		50.2 (40.8–58.6)	53.0 (45.7–60.2)
Women [n (%)]		281 (59.8)	68 (56.0)
High education [n (%)][¥]		161 (34.6)	29 (24.0)
Lifestyle characteristics			
BMI [kg/m^2, median (P25–P75)]		24.5 (22.5–26.9)	25.1 (23.4–27.1)
Current smokers [n (%)]		85 (18.1)	36 (29.5)
NSAID use [≥1x/week, n (%)]		42 (9.1)	10 (8.2)
Physical activity [high; n (%)]*		154 (33.4)	41 (34.5)
Medical characteristics			
MMR gene mutation [n (%)]	MLH1	178 (37.9)	49 (40.2)
	MSH2	192 (40.9)	55 (45.1)
	MSH6	95 (20.2)	17 (13.9)
	PMS2	3 (0.6)	1 (0.8)
History of cancer [n (%)]	CRC[$]	121 (25.7)	31 (25.4)
	Other cancer	82 (17.5)	26 (21.3)
History of colorectal neoplasms [n (%)][¶]		232 (49.4)	73 (59.8)
No. of colonoscopies during person time [n (%)]	1	179 (38.1)	70 (57.4)
	2	193 (41.1)	39 (32.0)
	≥3	95 (20.2)	10 (8.2)
Dietary supplement use[#]			
Any [n (%)]		188 (40.0)	54 (44.3)
Multivitamins [n (%)]		121 (25.7)	37 (30.3)
Vitamin C [n (%)]		61 (13.0)	17 (13.9)
Vitamin B complex [n (%)]		8 (1.7)	1 (0.8)
Vitamin E [n (%)]		9 (1.9)	1 (0.8)
Vitamin D [n (%)]		6 (1.3)	1 (0.8)
Folic acid [n (%)]		9 (1.9)	1 (0.8)
Calcium [n (%)]		22 (4.7)	6 (4.9)

Table 4.1 continues on next page

Table 4.1 *Continued*

	Total population (n=470)	Colorectal adenoma cases (n=122)
Iron [n (%)]	3 (0.6)	0
Fish oil [n (%)]	32 (6.8)	13 (10.7)
Other [n (%)]^	58 (12.3)	20 (16.4)
Dietary intake		
Total energy [kJ/day, mean ± SD]	9,055 ± 2,798	8,711 ± 2,702
Vegetables intake [g/day, median (P25–P75)]	123 (76–176)	124 (61–173)
Fruit intake [g/day, median (P25–P75)]	157 (75–234)	136 (44–234)
Red meat intake [(g/day, median (P25–P75)]	46 (30–64)	50 (30–67)
Alcohol intake [g/day, median (P25–P75)]	7.2 (1.5–16.8)	9.4 (3.2–21.8)

¥ College or university degree.
* Highest tertile of the physical activity score. [31]
$ CRC = colorectal cancer.
¶ History of colorectal adenoma and/or carcinoma.
# Use of any dietary supplement during the last month.
^ E.g. glucosamine/chondroitin supplements, and garlic pills.

Of the dietary supplement users, 28.7% developed a colorectal adenoma during the follow up period (**Table 4.2**); this was 24.1% in nonusers. Compared to nonusers, dietary supplement users were slightly older, were more often women, were more often higher educated, smoked less often, had more often a history of cancer or colorectal tumors, and consumed more fruit.

Table 4.2 General characteristics of the mismatch repair gene mutation carriers stratified by dietary supplement use in the GeoLynch cohort study

	Dietary supplement users		
	User¥ (n=188)	Nonusers* (n=282)	P-value‖
Person time [months, median (P25–P75)]	36.6 (24.4–49.4)	41.8 (26.0–50.2)	0.17
Demographic characteristics			
Age at study entry [years, median (P25–P75)]	51.7 (42.1–58.6)	48.9 (39.6–58.6)	0.17
Women [n (%)]	128 (68.1)	153 (54.3)	<0.01
High education [n (%)]$	70 (37.4)	91 (32.7)	0.59
Lifestyle characteristics			
BMI [kg/m^2, median (P25–P75)]	24.1 (21.9–26.3)	24.7 (22.9–27.5)	0.23
Current smokers [n (%)]	31 (16.5)	54 (19.2)	0.15
NSAID use [≥1x/week, n (%)]	17 (9.2)	25 (9.1)	0.97
Physical activity [high; n (%)]¶	63 (34.2)	91 (32.9)	0.76

Table 4.2 continues on next page

Table 4.2 *Continued*

		Dietary supplement users		
		User[¥] (n=188)	Nonusers* (n=282)	P-value[‖]
Medical characteristics				
MMR gene mutation [n (%)]	MLH1	76 (40.4)	102 (36.2)	0.27
	MSH2	66 (35.1)	126 (44.7)	
	MSH6	43 (22.9)	52 (18.4)	
	PMS2	2 (1.1)	1 (0.4)	
Colorectal adenoma cases during follow up [n (%)]		54 (28.7)	68 (24.1)	0.28
History of cancer [n (%)]	CRC[#]	50 (26.6)	71 (25.2)	0.73
	Other cancer	41 (21.8)	41 (14.5)	0.04
History of colorectal neoplasms [n (%)][^]		99 (52.7)	133 (47.2)	0.31
No. of colonoscopies during person time [n (%)]	1	69 (36.7)	110 (39.0)	0.83
	2	80 (42.6)	113 (40.1)	
	≥3	37 (19.7)	58 (20.6)	
Dietary supplement use[¥]				
Multivitamins [n (%)]		121 (64.4)	-	
Vitamin C [n (%)]		61 (32.5)	-	
Vitamin B complex [n (%)]		8 (4.3)	-	
Vitamin E [n (%)]		9 (4.8)	-	
Vitamin D [n (%)]		6 (3.2)	-	
Folic acid [n (%)]		9 (4.8)	-	
Calcium [n (%)]		22 (11.7)	-	
Iron [n (%)]		3 (1.6)	-	
Fish oil [n (%)]		32 (17.0)	-	
Other [n (%)][|]		58 (30.9)	-	
Dietary intake				
Total energy intake [kJ/day, mean ± SD]		8,871 ± 2,647	9,179 ± 2,893	0.36
Vegetables intake [g/day, median (P25–P75)]		123 (81–177)	125 (73–175)	0.61
Fruit intake [g/day, median (P25–P75)]		167 (79–235)	130 (53–233)	0.11
Red meat intake [(g/day, median (P25–P75)]		46 (27–63)	46 (34–64)	0.38
Alcohol intake [g/day, median (P25–P75)]		6.7 (1.6–16.3)	7.4 (1.5–17.1)	0.69

[¥] Use of any dietary supplement during the last month.
* No use of dietary supplement during the last month.
[$] College or university degree.
[¶] Highest tertile of the physical activity score. [31]
[#] CRC = colorectal cancer.
[^] History of colorectal adenoma and/or carcinoma.
[|] E.g. glucosamine/chondroitin supplements, and garlic pills.
[‖] Calculated using Mann-Whitney U test for continuous variables or the chi-square test for categorical variables.

Use of any dietary supplement was not statistically significantly associated with colorectal adenoma risk (HR=1.18; 95% CI 0.80–1.73) after adjustments for age, sex, and number of colonoscopies during person time (**Table 4.3**). In addition, no associations were found between colorectal adenomas and multivitamin supplement use (HR=1.15; 95% CI 0.72–1.84), vitamin C supplement use (HR=1.57; 95% CI 0.93–2.63), calcium supplement use (HR=0.69; 95% CI 0.25–1.92), and use of supplements containing fish oil (HR=1.60; 95% CI 0.79–3.23).

Table 4.3 Associations of dietary supplement use and colorectal adenoma risk in the GeoLynch cohort study of MMR gene mutation carriers

	No use[¥]	Use[*]
Dietary supplement use	HR	HR (95% CI)
Any dietary supplement		
No. of cases/non-cases	68/214	54/134
Person time (months, median)	41.8	36.6
HR, adjusted for age & sex	1.0	1.21 (0.85–1.72)
HR, adjusted for age, sex, and number of colonoscopies during person time	1.0	1.18 (0.80–1.73)
Multivitamins		
No. of cases/non-cases	85/264	37/84
Person time (months, median)	39.6	37.5
HR, adjusted for age & sex	1.0	1.38 (0.93–2.07)
HR, adjusted for age, sex, and number of colonoscopies during person time	1.0	1.15 (0.72–1.84)
Vitamin C		
No. of cases/non-cases	105/304	17/44
Person time (months, median)	39.9	34.5
HR, adjusted for age & sex	1.0	1.36 (0.80–2.31)
HR, adjusted for age, sex, and number of colonoscopies during person time	1.0	1.57 (0.93–2.63)
Calcium		
No. of cases/non-cases	116/332	6/16
Person time (months, median)	39.2	36.9
HR, adjusted for age & sex	1.0	0.68 (0.24–1.93)
HR, adjusted for age, sex, and number of colonoscopies during person time	1.0	0.69 (0.25–1.92)
Fish oil		
No. of cases/non-cases	109/329	13/19
Person time (months, median)	39.2	37.1
HR, adjusted for age & sex	1.0	1.74 (1.00–3.01)
HR, adjusted for age, sex, and number of colonoscopies during person time	1.0	1.60 (0.79–3.23)

[¥] No use of dietary supplements during the last month.
* Use of any dietary supplement during the last month.

In this study population, 73 of the 232 MMR carriers with a history of colorectal neoplasms before study entry developed a colorectal adenoma during follow up, of which 36 were dietary supplement user. In MMR carriers without a history of colorectal neoplasms (n=238), 49 subjects developed a colorectal adenoma of which 18 subjects used a dietary supplement. Among MMR carriers with a history of colorectal neoplasms, dietary supplement use was not statistically significantly associated with colorectal adenoma risk (HR=0.87; 95% CI 0.44–1.75). However, a borderline statistically significantly increased risk was observed for dietary supplement use and colorectal adenoma risk among those without a history of colorectal neoplasms (HR=1.60; 95% CI 0.98–2.60).

Table 4.4 shows that there is no effect measure modification with smoking status (P for multiplicative interaction: 0.41) and total fruit and vegetables intake (P for multiplicative interaction: 0.39) in the association of dietary supplement use and colorectal tumor risk. In a sensitivity analysis, in which person time started at the time of assessment of dietary supplement use, no differences in associations were observed for any use or use of specific types of dietary supplements and colorectal adenoma risk. However, a borderline statically significantly increased risk of colorectal adenomas was observed for persons who took supplements containing fish oil (HR=1.78; 95% CI 0.92–3.45).

DISCUSSION

The present study did not observe a statistically significant association between use of any dietary supplement and colorectal adenoma risk among individuals with Lynch syndrome. No marked associations were found for multivitamin supplement use, vitamin C supplement use, calcium supplement use, and use of supplements containing fish oil and colorectal adenoma risk either.

To our best knowledge, this is the first prospective cohort study that examined the association of dietary supplement use and development of colorectal adenomas in individuals with Lynch syndrome. The association between dietary supplement use and sporadic colorectal adenoma risk in the general population has been investigated in many epidemiological studies. [23-27] Our findings for dietary supplement use and colorectal adenoma risk in individuals with Lynch syndrome were largely consistent with findings in the general population. Calcium supplement use might contribute to a lower risk of colorectal adenomas in the general population. [27] However, no evidence of an

Table 4.4 Associations of any dietary supplement use and colorectal adenoma risk stratified for smoking status and total fruit and vegetables intake in the GeoLynch cohort study of MMR gene mutation carriers

	Smoking status			
Dietary supplement use	Never	Former	Current	
No use[¥]				
No. of cases/non-cases	17/99	28/83	23/31	
Person time (months, median)	46.0	44.9	31.0	
HR (95% CI) adjusted for age, sex, and number of colonoscopies during person time	1.0	1.54 (0.84–2.84)	2.54 (1.42–4.54)	
Use*				
No. of cases/non-cases	8/56	33/60	13/18	
Person time (months, median)	37.2	35.9	39.1	
HR (95% CI) adjusted for age, sex, and number of colonoscopies during person time	0.89 (0.39–2.00)	2.05 (1.10–3.82)	3.37 (1.59–7.13)	
P for multiplicative interaction				0.41
	Total fruit and vegetables intake (g/day)			
Dietary supplement use	<179	179–283	283–387	≥387
No use[¥]				
No. of cases/non-cases	26/51	10/60	15/51	18/51
Person time (months, median)	34.3	45.9	45.3	36.8
HR (95% CI) adjusted for age, sex, and number of colonoscopies during person time	1.0	0.48 (0.23–1.03)	0.88 (0.44–1.74)	0.78 (0.45–1.35)
Use*				
No. of cases/non-cases	16/25	13/34	14/38	14/34
Person time (months, median)	27.2	42.1	40.3	35.9
HR (95% CI) adjusted for age, sex, and number of colonoscopies during person time	1.25 (0.63–2.52)	0.97 (0.45–2.08)	0.96 (0.45–2.03)	0.66 (0.29–1.50)
P for multiplicative interaction				0.39

[¥] No use of dietary supplements during the last month.
* Use of any dietary supplement during the last month.

association was found for calcium supplement use and colorectal adenoma risk in this Lynch syndrome population. A randomized, double-blind, placebo-controlled trial with calcium supplements, conducted in 30 first-degree relatives of Lynch syndrome patients, showed a small but nonstatistically significant reduction in epithelial cell proliferation in biopsies of the rectum, and no effect in the sigmoid and descending colon compared with placebo after 12 weeks of intervention. [32] Those results also do not suggest that the use of calcium supplements may help to lower the increased risk of colorectal adenoma occurrence among mismatch repair gene carriers.

No significant association was shown for fish oil supplements and colorectal adenoma risk, when person time started at the date of the most recent colonoscopy before assessment of dietary supplement use. However, according to sensitivity analyses when person time started at the time of assessment of dietary supplement use, a borderline statistically significantly increased risk for colorectal adenomas was observed for Lynch syndrome patients who took fish oil supplements. Our findings should be interpreted with caution, as our hazard ratios appear to be unstable, probably due to the low number of fish oil supplement users in our study. Moreover, the possible detrimental role of supplements containing fish oil on colorectal tumor risk in Lynch syndrome patients contrasts with findings in the general population: fish oil, and then particularly n-3 PUFA from fish oil, are thought to play a beneficial role in the prevention of colorectal cancer due to its anti-angiogenic and anti-inflammatory properties and its regulatory role in cell proliferation and apoptosis. [33-36] Nevertheless, the potentially increased risk for developing colorectal adenomas due to supplements containing fish oil in our study corresponds with findings in a nested case-control study within the VITamins And Lifestyle cohort. High intake of n-3 PUFA from diet plus supplements was associated with a decreased risk of colorectal cancer among those at low genetic risk (HR=0.23; 95% CI 0.07–0.78), while such intake was associated with a substantially increased risk among those at high genetic risk (HR=5.79; 95% CI 1.79–18.7). Genetic risk was calculated using a genetic risk score enumerating the number of risk alleles present at 16 single nucleotide polymorphisms (SNPs) located within known/recently-identified CRC susceptibility loci. [37] Expansion of our Lynch syndrome cohort and a longer follow up are essential to further investigate the role of fish oil supplements and colorectal adenoma risk.

Stratified analyses for MMR carriers with and without a history of colorectal neoplasms before study entry showed no association for dietary supplement use and colorectal adenoma risk among those without a history of colorectal neoplasms, whereas a borderline statistically significantly increased risk was observed for MMR carriers with a history of

colorectal neoplasms. Due to the low number of users reflected in the wide confidence intervals in this study, we are not able to draw firm conclusions considering differences between these two groups.

Several critical points regarding the study design and dietary supplement use need to be highlighted. The combined analysis of all the different kinds of dietary supplements on colorectal adenoma risk may mask individual effects of each nutrient supplement. Although this study is the largest prospective study in MMR gene mutation carriers up until now, the small number of users of individual dietary supplements in our study narrows the extent to which we can observe associations.

MMR gene mutation carriers might have increased their dietary supplement intake based on their health status and risk, [28] and may therefore have a higher use of dietary supplements compared to the general Dutch population. However, dietary supplement use in this Lynch syndrome population was similar (40%) to the general Dutch population (30–56%); also in our study dietary supplement users were more often women. [38] Moreover, we relied on self-reporting which makes misclassification of dietary supplement use possible. However, according to several studies, self-reported dietary supplement use is a reliable method to measure intake of dietary supplements. [39-41] Thus, dietary supplement use in individuals with Lynch syndrome included in this study reflects use in the general Dutch population and is a reliable indicator for the actual intake.

As information on dosage and duration was not assessed, we could not calculate the total nutrient intake by foods and dietary supplements together, and were unable to examine changes in dietary supplement use over time. Our data only allowed us to examine the associations for dietary supplement use as it was reported before the events of interest.

Strengths of this study are the inclusion of confirmed MMR gene mutation carriers in our cohort, and the high participation rate of 73%. These factors make our findings generalizable to Lynch syndrome patients in comparable clinical settings. Other strengths are the prospective cohort design, the relatively long person time, and the ability to adjust for many potential confounders.

In conclusion, in this prospective cohort study no associations between dietary supplement use and colorectal adenoma risk among individuals with Lynch syndrome were indicated. Further research is warranted to determine whether or not dietary supplement use is associated with colorectal adenoma and colorectal cancer risk in MMR gene mutation carriers.

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Chapter 5

The COLON study: Colorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival and quality of life

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ABSTRACT

Background There is clear evidence that nutrition and lifestyle can modify colorectal cancer risk. However, it is not clear if those factors can affect colorectal cancer treatment, recurrence, survival and quality of life. This paper describes the background and design of the "COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival and quality of life" – COLON – study. The main aim of this study is to assess associations of diet and other lifestyle factors, with colorectal cancer recurrence, survival and quality of life. We extensively investigate diet and lifestyle of colorectal cancer patients at diagnosis and during the following years; this design paper focuses on the initial exposures of interest: diet and dietary supplement use, body composition, nutrient status (e.g. vitamin D), and composition of the gut microbiota.

Methods and design The COLON study is a multicenter prospective cohort study among at least 1,000 incident colorectal cancer patients recruited from 11 hospitals in the Netherlands. Patients with colorectal cancer are invited upon diagnosis. Upon recruitment at diagnosis, and 6 months, 2 years and 5 years post-diagnosis, patients fill out food frequency questionnaires; questionnaires about dietary supplement use, physical activity, weight, height, and quality of life; and donate blood samples. Diagnostic CT-scans are collected to assess cross-sectional areas of skeletal muscle, subcutaneous fat, visceral fat and intermuscular fat, and to assess muscle attenuation. Blood samples are biobanked to facilitate future analyses of biomarkers, nutrients, DNA etcetera. Analysis of serum 25-hydroxy vitamin D levels, and analysis of metabolomic profiles are scheduled. A subgroup of patients with colon cancer is asked to provide faecal samples before and at several time points after colon resection to study changes in gut microbiota during treatment. For all patients, information on vital status is retrieved by linkage with national registries. Information on clinical characteristics is gathered from linkage with the Netherlands Cancer Registry and with hospital databases. Hazards ratios will be calculated for dietary and lifestyle factors at diagnosis in relation to recurrence and survival. Repeated measures analyses will be performed to assess changes over time in diet, lifestyle, and other factors in relation to recurrence and survival.

INTRODUCTION

Colorectal cancer is the third most common type of cancer worldwide. [1] Lifestyle and nutritional factors influence colorectal cancer risk. High consumption of red and processed meat and alcoholic beverages and low consumption of foods containing dietary fiber convincingly increase the risk of colorectal cancer. Body fatness – especially abdominal fatness –, and adult attained height increase the risk of colorectal cancer, while physical activity protects against colorectal cancer. [2,3]

In contrast to the extensive knowledge on the role of nutrition and lifestyle in the prevention of colorectal cancer, much less is known about the role of diet and lifestyle during and after treatment of colorectal cancer. Few prospective studies reported on factors that were associated with colorectal cancer recurrence and survival, while those studies were often hampered by the fact that dietary assessment was retrospective, that patient groups were small and heterogeneous, or that other prognostic factors were not taken into account. [4] Evidence-based lifestyle recommendations are necessary for the increasing number of colorectal cancer survivors, since these survivors may show a major interest in adjusting their usual habits. [5-7] The aim of the current study is to further explore the association between diet and other lifestyle factors in colorectal cancer prognosis, survival and quality of life, with special emphasis for the role of diet and dietary supplement use, body composition, nutrient status, and composition of the gut microbiota.

Few prospective studies assessed the association between diet and dietary supplement use and colorectal cancer prognosis and survival. An observational study within a randomized controlled chemotherapy trial (n=1,009 stage III colorectal cancer patients), [8] showed that colorectal cancer patients who scored high on a diet that could be described as a Western diet, with high intakes of meat, fat, refined grains, and desserts, had a 3 times higher risk of cancer recurrence or death (HR=3.25; 95% CI 2.04–5.19) than persons who scored low on such a pattern. Conversely, a prudent pattern, high in vegetables, fruits, poultry, and fish, was not associated with colorectal cancer outcomes in that study. There are only few additional publications on diet and colorectal cancer outcomes. [4] It is unclear if the use of dietary supplements by colorectal cancer patients affects colorectal cancer recurrence and survival. Dietary supplement use among patients has been assessed in several – mainly US – studies and is estimated to be as high as 60–80%. [9] An observational study, again within a randomized controlled chemotherapy trial (n=1,038 stage III colon cancer patients) showed that multivitamin use during and after adjuvant chemotherapy was not significantly

associated with outcomes in patients with stage III colon cancer. [10] It has been hypothesized that folic acid supplementation, may be involved in progression of established neoplasms. [11] This stresses the need to further address the role of dietary supplement use during and after colorectal cancer treatment.

Some data suggest that colorectal cancer patients who are obese or underweight may experience higher mortality rates than normal and overweight patients. [4,12-15] However, study results are not consistent. Underweight, overweight and obesity are usually only assessed by measuring the body mass index (BMI), [16-18] while BMI is not a valid measure for fat distribution or body composition. [19] Muscle depletion – assessed from diagnostic computed tomography (CT)-scans – has been associated with worse survival in a mixed groups of cancer patients (n=1,400), independently of BMI. [20] Moreover, among obese patients, those who are sarcopenic – i.e. those with severe muscle depletion – appear to have worse survival than patients who are not sarcopenic. [21] This warrants further study on the association between muscle mass, fat mass and survival among cancer patients. In addition, fat distribution of abdominal fat is an area that requires further investigation. Abdominal fat is mainly divided into two depots: subcutaneous and intra-abdominal or visceral fat. Visceral fat accumulation has been associated with increased incidence of colorectal cancer; [5] its association with recurrence of colorectal cancer has only sparsely been studied in small studies with short follow-up. [22-25] Nevertheless, those studies suggest that increased visceral fat areas, or an increased visceral fat versus subcutaneous fat ratio may increase the risk of recurrence. Visceral adiposity may also unfavourably affect colorectal cancer survival, but again this has only been studied in small populations (50–200 patients) with short follow-up and mostly in patients with metastatic disease; [22-24,26] results were therefore not conclusive. Concluding, the associations of body composition and fat distribution with recurrence and survival of colorectal cancer patients are promising areas of investigation.

Nutrient status at diagnosis as well as during treatment may also affect recurrence and survival. For instance, the role of vitamin D in colorectal cancer prevention and survival has gained much interest in recent years. A recent meta-analysis suggested that higher 25(OH)D levels (>75 nmol/L) were associated with significantly reduced mortality in patients with colorectal cancer. [27] Results should be interpreted with caution, as the assessment of 25(OH)D levels differed between the individual studies of the meta-analysis (pre versus post-diagnostic). Moreover, most studies only have one measurement of vitamin D levels, while cancer treatment and stage of disease may have a large impact on vitamin D status. Thus, cohort studies with repeated measurement of vitamin D levels are urgently needed.

Many colorectal cancer patients treated with chemotherapy suffer from mucositis and gastrointestinal complaints, such as severe diarrhea, nausea and vomiting. [28,29] Knowledge on the role of the gut microbiota – a major compartment of the gastrointestinal tract – in human health has emerged in the past years. [30] Yet, the gut microbiota has been relatively ignored in studies focusing on the pathophysiology and side effects of cancer therapies. [31] There is some evidence that chemotherapy induces a large decline in the diversity of the gut microbiota. [32,33] To what extent colorectal cancer patients receiving chemotherapy experience similar declines in diversity and whether diet and lifestyle affect recovery of the gut microbiota during and after chemotherapy is largely unknown.

In this study, we will assess associations of diet and other lifestyle factors, with colorectal cancer recurrence and survival and with quality of life. We comprehensively investigate diet and lifestyle of colorectal cancer patients at diagnosis and during the following years. This design paper focuses on the four initial topics of interest in this prospective cohort study: diet and dietary supplement use, body composition, nutrient status (e.g. vitamin D), and composition of the gut microbiota.

METHODS AND DESIGN

The "**Co**lorectal cancer: **L**ongitudinal, **O**bservational study on **N**utritional and lifestyle factors that influence colorectal tumor recurrence, survival and quality of life" – COLON – study is a prospective observational cohort study that aims to include at least 1,000 colorectal cancer patients from regional and academic hospitals in the Netherlands over a period of ~5 years. Ethical approval for the study was granted by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen (Commissie Mensgebonden Onderzoek – CMO, region Arnhem Nijmegen).

Recruitment

Men and women of all ages, who were newly diagnosed with colorectal cancer (ICD codes C18–20) in any stage of the disease in one of the 11 participating hospitals, are eligible for the study. Non-Dutch speaking patients, or patients with a history of colorectal cancer or (partial) bowel resection, chronic inflammatory bowel disease, hereditary colorectal cancer syndromes (Lynch syndrome, FAP, Peutz-Jegher), dementia or another mental condition that makes it impossible to fill out questionnaires correctly, will be excluded

from the study. Recruitment is conducted in close cooperation with staff of the oncology, gastroenterology and/or internal medicine departments of the participating hospitals. Recruitment procedures vary slightly per hospital. In general, eligible patients receive an information leaflet about the COLON study from their treating physician or from the nurse-practitioner shortly after diagnosis during a routine clinical visit. Patients can consult with their physician or nurse-practitioner, with a member of the study team, and/or with an independent physician if they have questions about the study. Patients who agree to participate have to provide written informed consent.

Data collection

Patients are asked to fill out several questionnaires upon recruitment at diagnosis, and at 6 months, 2 years and 5 years post-diagnosis (**Figure 5.1**). In addition, participants are asked to donate a blood sample at each time point. Patients who are treated with chemotherapy, are asked to additionally fill out questionnaires and to donate an extra blood sample 1 year after recruitment. At that point in time most of those patients will have completed their treatment, while other patients will have finished their treatment within 6 months. Patients are asked for permission for collection of paraffin-embedded tumor material using the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA).

Demographic and health characteristics

Demographic and health characteristics are assessed with a self-administered lifestyle questionnaire containing questions on demographics (education, ethnicity, living situation, number of children), body weight and height, history of body weight, smoking habits, history of medication (including use of aspirin and other NSAIDs), family history of cancer, any changes that patients made to their diet because of bowel complaints or other reasons, type of (alternative) treatment, experienced side effects of treatment, comorbidities, and for women: menopausal status, menstrual and reproductive history.

Dietary intake & dietary supplement use

Habitual dietary intake in the month preceding diagnosis – and for the other time points during the preceding month –, is assessed using a semi-quantitative food frequency questionnaire. This questionnaire was previously validated, [34,35] and slightly adapted to be

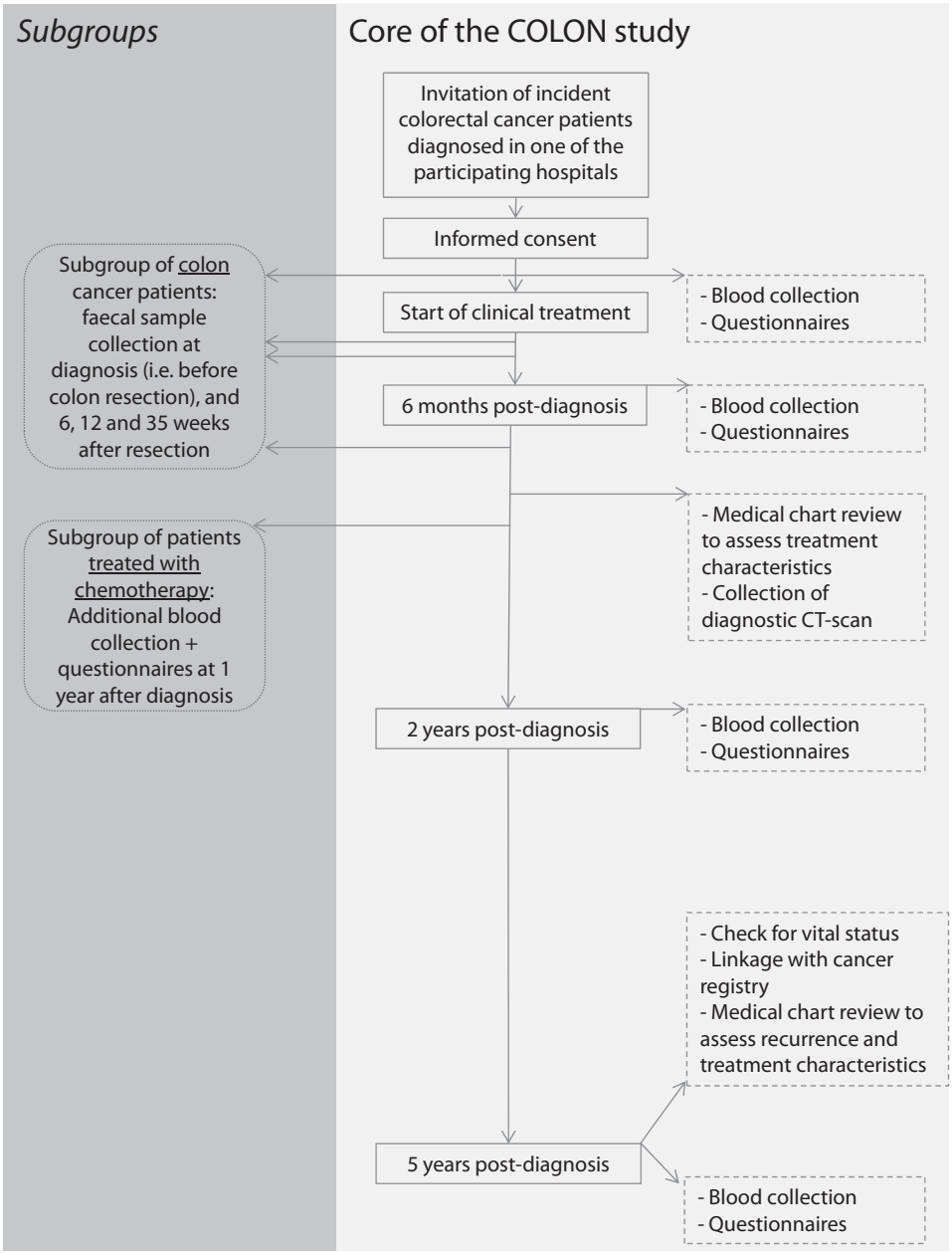

Figure 5.1 Overview and design of the COLON study.

able to distinguish meat intake with respect to red, processed, and white meat, and for dairy intake to be able to distinguish fermented and unfermented dairy. For all items, frequencies per day and standard portion sizes will be multiplied to obtain intake in grams per day.

Energy intake and nutrient intakes will be calculated using the Dutch food composition table. [36] Additionally, the food frequency questionnaire contains questions on the use of organic foods, i.e. the type of organic foods and the frequency of use.

Dietary supplement use is assessed using a self-administered dietary supplement questionnaire developed by the Division of Human Nutrition of Wageningen University, the Netherlands. The dietary supplement questionnaire contains questions on use of multivitamin/minerals supplements and other combinations not classified as multivitamins/minerals (e.g. vitamin B-complex, combination of antioxidants, combination of vitamin A/D, combination of calcium/magnesium/zinc, other combinations), and supplemental vitamin A, folic acid, vitamin B12, vitamin C, vitamin D, vitamin E, calcium, magnesium, zinc, iron, selenium, chrome, fish oil, and herbal and specialty supplements, and on the dosage and frequency of intake. Upon recruitment, participants are asked whether they used any dietary supplement during the year before colorectal cancer diagnosis. At the other time points, dietary supplement use in the period since the last questionnaire is enquired.

Body composition

Patients are asked to measure and report their waist and hip circumference; instructions and a measuring device are provided. In addition, CT-images are retrieved from medical records of all participants for the assessment of body composition. Diagnostic CT-images are available from almost all colorectal cancer patients (~85–90%), as they are used for diagnosis and staging of the disease. From these CT-images, cross-sectional areas (cm^2) of skeletal muscle, subcutaneous fat, visceral fat and intermuscular fat will be quantified at the landmark level of the third lumbar vertebra (L3) using Slice-O-matic software (Tomovision, Canada). Cross-sectional L3 adipose and muscle areas are linearly related to total body adipose and muscle mass. [37-39]

Physical activity

Self-reported physical activity is assessed using the Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH). [40] The general purpose of this questionnaire is to assess habitual physical activity, with a reference period of a normal week in the past months. Participants are asked to report their average time spend on the following prestructured types of activities: commuting activities, activity at work, household activities

and leisure time activities (walking, bicycling, gardening, odd jobs and up to four sports). The SQUASH consists of three main queries: days per week, average time per day, and intensity. The recorded activity will be converted into Metabolic Equivalent (MET)-scores using the Compendium of Physical Activities. [41] Validation studies [40,42,43] showed that the SQUASH-questionnaire is fairly reliable and reasonably valid in an adult population and may be used to rank participants based on their physical activity level and to categorize them according to the Dutch physical activity guideline (30 minutes or more of at least moderate intense physical activity for a minimum of 5 days per week).

Blood sample collection and analysis

Nonfasting blood samples are drawn from patients upon recruitment and at all later time points during a regular clinical visit of the patient. The baseline blood sample is preferably taken before surgery or start of treatment. In case of neo-adjuvant radiation therapy, it is not always possible to draw blood before the start of treatment, and for those patients a blood sample is collected before surgery. For each blood sample, haematocrit is assessed immediately after blood draw at all study sites. Blood samples are processed into serum (6 aliquots), plasma (5 aliquots), full blood (2 aliquots), and buffy coat (2 aliquots) and stored in a biobank at -80°C. All procedures are defined in a protocol in order to ensure standardization over study sites. Blood samples are biobanked for later analysis of metabolites, biomarkers, nutrients etc. Analysis of 25-hydroxy vitamin D is already anticipated; in addition, metabolomics will be performed. Both 25-hydroxy vitamin D2 and 25-hydroxy vitamin D3 levels will be assessed in serum samples using a liquid chromatography tandem mass spectrometry method. [44] In a subset of the patients targeted and untargeted metabolomic analysis will be performed using the Biocrates AbsoluteIDQ p180 Kit for the targeted approach and UPLC-ESI-qTOF for the untargeted approach at the IARC, France.

Faecal sample collection and analysis

In order to assess whether cancer therapy affects composition and function of the gut microbiota in colon cancer patients, faecal samples are collected from a subgroup of patients with colon cancer who are diagnosed in one of the participating hospitals (Hospital Gelderse Vallei, Ede). Faecal samples are collected shortly after diagnosis (i.e. before colon resection), and 6, 12 and 35 weeks after resection. For patients who are

treated with chemotherapy, this corresponds to sample collection before, during and after chemotherapy. A phylogenetic microarray (the Human Intestinal Tract Chip; HITChip) will be used for a high-throughput characterisation of the composition of the gut microbiota. [45]

Clinical outcome measurements

Information on clinical factors are retrieved from linkage with the Netherlands Cancer Registry and will include pathologic and clinical disease stage (TNM), date of colorectal cancer incidence, location of the tumor, morphology, degree of differentiation, number of lymph nodes surgically sampled and number of positive lymph nodes, type and date of surgery, surgical complications (anastomotic leakage, abscess), tumor residue, type of treatment (chemotherapy, radiotherapy, chemoradiation, other) and date of start treatment, location of metastases (ICD-code) and distance of tumor from anus (rectal tumors only). Additional clinical data will be retrieved from medical record abstraction. We are using standardized forms and methods to abstract the medical records for all of the participants at regular intervals during the cohort study. Medical variables include history of gastro-intestinal disease, date and indication for endoscopy at diagnosis, length of hospital stay after primary surgery, body weight and height, size of the tumor, length of surgically removed bowel, CEA level, all treatment and follow-up care including data on chemotherapy and radiation therapy, adenoma/carcinoma recurrence.

The main outcomes of this cohort are treatment completion rates, side effects of treatment, disease outcomes and quality of life. Disease outcomes are colorectal cancer recurrence, colorectal adenoma occurrence/recurrence and survival/mortality. Information on mortality/survival is gathered from linkage with the civil municipalities registry (in Dutch: Basisregistratie personen), information on cause of death is ascertained by linkage with Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek).

Assessment of quality of life

Quality of life is assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 version 3.0 (EORTC QLQ-C30), which is a widely used measure of Health-Related Quality of Life in cancer. [46,47] The questionnaire contains five functioning scales (physical, role, cognitive, emotional, and social functioning); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and health

related quality of life scale. Patient-reported chemotherapy-induced peripheral neuropathy is assessed in patients treated with chemotherapy using the "Quality of Life Questionnaire-CIPN twenty-item scale" (QLQ-CIPN20); this questionnaire is provided at the 1 year time point. [48,49] This 20 item questionnaire includes three scales assessing sensory, motor and autonomic symptoms that can result from neuropathy.

An individual's coping style is assessed with the "Coping Inventory for Stressful Situations" – CISS – questionnaire, [50] a valid and reliable tool to assess basic coping styles. This inventory measures three different coping styles: task-oriented, emotion-oriented and avoidance-oriented coping. Coping style is only assessed at the 2 year time point, as this is considered to be a stable factor that will not change over time.

Power considerations and data analysis

A prospective cohort study assesses multiple exposures and outcomes. The power calculation for this cohort study was based on one exposure that was of special interest in this study – i.e. dietary supplement use – and the anticipated association with recurrence of colorectal cancer and survival. There are few publications on the prevalence of dietary supplement use in the general population in the Netherlands, or among colorectal cancer patients; therefore, we assume that supplement use in patients is comparable to supplement use in the general elderly population: ~45%. [51]

Our aim is to include at least 1,000 patients in our study. After 5 years of follow-up, we expect a number of 320 recurrences and 250 deaths. [8,52] This will enable us to detect the following associations: for recurrences, a HR of ≤0.78 or ≥1.31 (alpha=0.05 and power=0.8), and for mortality, a HR of ≤0.77 or ≥1.33 (alpha=0.05 and power=0.8).

Cox proportional hazard models will be used to calculate hazard ratios for dietary and lifestyle factors at diagnosis in relation to outcomes. Changes of dietary and lifestyle factors over time will be analyzed with analysis techniques for longitudinal data, since the observations of one individual over time are not independent.

All associations will be adjusted for age and sex and if applicable for stage of the disease. Additionally, we will check whether other additional variables should be included in the multivariate models as potential confounding variables and/or effect measure modifiers.

DISCUSSION

This is the largest prospective European study among colorectal cancer patients with repeated information on a variety of dietary and lifestyle factors and other exposures. Recruitment is expected to be complete by the beginning of 2015. This prospective cohort study will shed further light on the associations between diet, other lifestyle factors and quality of life, recurrence and survival among colorectal cancer patients.

Although this is the largest European prospective study so far, even larger studies are necessary for specific analyses in subgroups of patients, e.g. within stages of disease, or within groups of patients with the same treatment. Therefore, we have harmonized our study protocol with two other ongoing prospective studies among colorectal cancer patients: the EnCoRe study of Maastricht University, the Netherlands, [53] and with the ColoCare Study of the German Cancer Research Center in Heidelberg. [54] Thus, in future collaborations, we can pool the results of these studies to be able to increase the power; the expected number of patients in all three cohorts will be at least 2,200.

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Chapter 6

Consistency of dietary supplement use among colorectal cancer patients from diagnosis until two years post-diagnosis

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ABSTRACT

Background Dietary supplement use among colorectal cancer patients is common, but use may not necessarily be beneficial. However, it is unknown whether use changes after diagnosis. In this prospective cohort study among colorectal cancer patients, the consistency of dietary supplement use from diagnosis until two years post-diagnosis was assessed.

Methods and materials Colorectal cancer patients filled out detailed self-administered questionnaires on dietary supplement use at diagnosis, six months and two years post-diagnosis. Current use was defined as use of any dietary supplement at least once per week during the preceding month. Patients were categorised into consistent nonusers (no use at all three time points), inconsistent users (difference in use or no use between the three time points), and consistent users (use at all three time points).

Results Among 160 colorectal cancer patients, 61 (38.1%) used dietary supplements at diagnosis, while the prevalence of use was 81 (50.6%) and 62 (38.8%) at six months and two years post-diagnosis respectively. Among 21.3% of the patients, use was consistent over time, 43.8% reported inconsistent use, and 35.0% reported not to use supplements at any of the three time points. Also, patients took different types of supplements over time. Characteristics of consistent users were similar to inconsistent users and consistent nonusers.

Conclusion We observed that dietary supplement use among colorectal cancer patients was common, but use changed during and after cancer therapy. Observational studies among colorectal cancer patients should repetitively assess use after cancer diagnosis in order to obtain a good estimate of dietary supplement use.

INTRODUCTION

Expert guidelines formulated by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) advise against the use of dietary supplements for cancer prevention and survival, and recommend to meet nutritional needs through diet alone. [1] However, these guidelines are mainly based on randomized controlled trials reporting that dietary supplement use may exert unexpected adverse effects in particular for individuals with a high risk of (pre)cancerous lesions. [1] Use of dietary supplements is also discouraged for cancer patients, because potential interactions with conventional cancer treatments may occur. [2-11] Furthermore, it is recommended that cancer patients should only take medically indicated supplements under the guidance of their clinician. [12] However, clinicians are often not aware of their patients' use of commercially available supplements after cancer diagnosis, because those patients do not always communicate with their clinician about their use. [13-17] As it is still inconclusive whether use of dietary supplements may have favorable or unfavorable effects for those diagnosed with cancer, [18-20] such as patients with colorectal cancer, these aspects are a matter of concern.

Colorectal cancer patients commonly report that they start taking dietary supplements directly after diagnosis, [21-25] during or after cancer therapy, [22,24-27] or that they start taking additional dietary supplements [21,28] with the belief to improve their prognosis, overall health, and quality of life. [26,28-32] However, most studies among colorectal cancer patients assessed dietary supplement use at one point in time, mostly at time of diagnosis [23-25,28] assuming that use after diagnosis, during or after cancer therapy is stable. Before the association between dietary supplement use and colorectal cancer prognosis can be examined, more information is needed about the consistency of use over time, as it is plausible that use after cancer diagnosis may change. [33]

Studies that assessed dietary supplement use repetitively over time are scarce. In the United States, a prospective observational study among stage III colon cancer patients reported that 40% of the patients were consistent multivitamin users during and six months after adjuvant chemotherapy, 34% were inconsistent users and 26% were nonusers. [34] Furthermore, data from the Colon Cancer Family Registry showed substantial increases in the use of folic acid containing supplements after a diagnosis of colorectal cancer (55.1%) compared to before diagnosis (35.4%), while one fourth of the cases who were already using those supplements before diagnosis stopped use 5 years post-diagnosis. [27] Data from another American cohort among colon cancer patients showed that dietary supplement use was almost three times

higher two years post-diagnosis compared to use at diagnosis. [25] These American studies among colon cancer patients examined consistency of use at two time points, but they did not examine use across several time points after diagnosis, during and after cancer therapy.

In Europe, dietary supplement use is lower than in the US, differs between countries [35] and varies over time in the general population. [33,36] However, no studies about the consistency of use are available among colorectal cancer patients. Therefore, the main objective of this prospective cohort study in the Netherlands, a country with a relatively low and infrequent use of dietary supplements, [37] was to describe the consistency of dietary supplement use among colorectal cancer patients from diagnosis until two years post-diagnosis.

METHODS AND MATERIALS

Study design and study population

Details of this ongoing prospective cohort study among colorectal cancer patients (the COLON study) have been described earlier. [38] In short, primary diagnosed colorectal cancer patients are recruited directly after diagnosis during a routine clinical visit before surgery in eleven participating hospitals in the Netherlands, and are prospectively followed during and after cancer therapy. Men and women of all ages, who are in any stage of the disease of colorectal cancer, are eligible for the study. Non-Dutch speaking patients, or patients with a history of colorectal cancer or (partial) bowel resection, chronic inflammatory bowel disease, hereditary colorectal cancer syndromes (i.e. Lynch syndrome, FAP, Peutz-Jegher), dementia or another mental condition that makes it impossible to fill out a questionnaire correctly, are excluded from the study.

For the current study, information on diet, lifestyle and medical characteristics from diagnosis until two years post-diagnosis is needed in order to examine the consistency of dietary supplement use. Of the 366 colorectal cancer patients included until 31 December 2012, 25 colorectal cancer patients died, and 67 patients were lost to follow-up. Unfortunately, 114 patients had no data from two years post-diagnosis yet. Thus, the total population of this study consisted of 160 colorectal cancer patients with complete data at colorectal cancer diagnosis, six months and two years post-diagnosis.

To estimate the response rate for the number of patients who participated in the study compared to the total number of patients who were initially invited, we linked our database

to the Dutch Cancer Registry. Based on this registration, we estimated that the response rate was about ~40–70% among those eligible depending on hospital. All participants gave written informed consent. Approval of the study was obtained by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen (Commissie Mensgebonden Onderzoek – CMO, region Arnhem Nijmegen) in the Netherlands.

Assessment of dietary supplement use

Upon recruitment at colorectal cancer diagnosis, six months and two years post-diagnosis, dietary supplement use in the COLON study was assessed with a self-administered dietary supplement questionnaire developed by the Division of Human Nutrition of Wageningen University, the Netherlands. The questionnaire contained questions on use of multivitamin/minerals supplements or other supplements containing a combination of at least two vitamins and/or minerals (e.g. vitamin B-complex, combination of antioxidants, combination of vitamin A/D, combination of calcium/magnesium/zinc, other combinations), and supplemental vitamin A, folic acid, vitamin B12, vitamin C, vitamin D, vitamin E, calcium, magnesium, zinc, iron, selenium, chrome, fish oil, and herbal and specialty supplements. Participants were asked whether they had used any dietary supplement during the last month. Participants reported the type of supplement, frequency of intake (<1 day per month, 1 day per month, 2–3 days per month, 1 day per week, 2–3 days per week, 4–5 days per week, 6–7 days per week), amount of intake (1, 2, 3, 4, >5 tablets or capsules), brand name, dosage (in mcg, mg or IU), and ingredients. Participants were considered as dietary supplement user when they used any dietary supplement at least once per week during the last month. When participants did not use any dietary supplement at least once per week during the last month, they were considered nonusers. Furthermore, we assessed the consistency of use over time. In those analyses, consistent nonusers were defined as subjects reporting no supplement use at diagnosis, six months and two years post-diagnosis, inconsistent users were defined as subjects reporting differences in supplement use or no use at diagnosis, six months or two years post-diagnosis, and consistent users were defined as subjects reporting supplement use at diagnosis, six months and two years post-diagnosis.

Assessment of dietary and lifestyle factors

Self-administered questionnaires on diet and lifestyle are filled out by the participants at colorectal cancer diagnosis, six months and two years post-diagnosis. Habitual dietary intake in the previous month is assessed with an updated version of a previously validated semi-quantitative food frequency questionnaire. [39,40] Information on demographic, anthropometric, and lifestyle factors is collected through a structured questionnaire containing questions about age, sex, height, weight, education, smoking, medication use, family history of cancer, and medical history. Information on physical activity is obtained with a short questionnaire to assess health-enhancing physical activity (SQUASH). [41] For these analyses, we determined whether participants were compliant to the Dutch physical activity guidelines, i.e. being physically active for minimal 30 minutes per day of at least moderate intensity for five or more days per week. [42] Moderate intensity activity was indicated as ≥4 metabolic equivalents for adults aged 18 to 55 years, and as ≥3 metabolic equivalents for adults aged 55+ years. [42]

Assessment of disease related characteristics

Incident colorectal cancer cases were confirmed by pathology reports obtained via the participating hospitals. From every participant, information on medical history and clinical characteristics of colorectal cancer (disease stage, location of the tumor, tumor type, and cancer therapy) was collected. Information on mortality is gathered by linkage to the civil municipality registries.

Descriptive statistics of the study population

For the total population (n=160), sociodemographic and disease related characteristics were presented. Furthermore, descriptive data for dietary supplement use were shown at colorectal cancer diagnosis, six months and two years post-diagnosis. In addition, the consistency of dietary supplement use was described, and changes in the number of supplements used over time were depicted. Sociodemographic and disease related characteristics, and dietary and lifestyle factors (means ± standard deviation, medians and interquartile range (IQR) or percentages) were reported for consistent nonusers, inconsistent and consistent users. A two-sided $P<0.05$ was considered statistically significant. SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used to perform all analyses.

RESULTS

The total population for these analyses consisted of 160 colorectal cancer patients with complete data on dietary supplement use directly after diagnosis, six months and two years post-diagnosis. Upon recruitment (**Table 6.1**), the mean age (± SD) at study entry of the total study population was 65.6 (± 9.7) years, 40.6% were women, and nearly one third was higher educated. Tumors were mainly located in the colon (62.5%), and the majority presented with stage I (27.5%), stage II (33.8%), or stage III (28.8%) of the disease. Most participants were treated with surgery only (45.6%) or surgery plus chemotherapy (26.3%). The population included in the analyses was similar to the total population of colorectal cancer patients included in the COLON study by December 2012 (data not shown).

Table 6.1 Sociodemographic and disease related characteristics in a prospective cohort study among colorectal cancer patients

	Total population (n=160)	
Sociodemographic characteristics		
Age at study entry [mean (SD)]	65.6	(9.7)
Women [n (%)]	65	(40.6)
High educational level [n (%)]	42	(26.3)
Family history of cancer [n (%)]¥	117	(73.1)
Disease related characteristics		
Disease stage [n (%)]¥		
Stage I	44	(27.5)
Stage II	54	(33.8)
Stage III	46	(28.8)
Stage IV	4	(2.5)
Tumor type [n (%)]¥		
Adenocarcinoma	141	(88.1)
Other	15	(9.4)
Location of the tumor [n (%)]¥		
Colon	100	(62.5)
Rectum	60	(37.5)
Therapy [n (%)]		
Surgery only	73	(45.6)
Surgery plus radiotherapy	20	(12.5)
Surgery plus chemotherapy	42	(26.3)
Surgery plus chemoradiation	20	(12.5)
Surgery plus radiotherapy plus chemotherapy	4	(2.5)
Other	1	(0.6)

¥ <5% missing.

Dietary supplement use at diagnosis, six months and two years post-diagnosis

Among 160 colorectal cancer patients, 61 (38.1%) of the patients used dietary supplements at diagnosis, while use was prevalent in 81 (50.6%) and 62 (38.8%) of the patients at six months and two years post-diagnosis respectively (**Table 6.2**). Multivitamins were the most commonly reported supplements at colorectal cancer diagnosis (54.1%), six months (48.2%) and two years post-diagnosis (58.1%). In contrast to colorectal cancer diagnosis (11.5%) or two years post-diagnosis (9.7%), use of magnesium supplements increased six months post-diagnosis (22.2%). Furthermore, intake of fish oil supplements decreased six months after the diagnosis (8.6% versus 18.0% at diagnosis and 16.1% two years post-diagnosis). Also, use of herbal and specialty supplements was lower six months post-diagnosis (16.0%) compared to diagnosis (29.5%) and two years post-diagnosis (41.9%). At colorectal cancer diagnosis, 55.6% of the users took one supplement at least once per week during the last month, while this was 71.6% and 61.3% at six months and two years post-diagnosis respectively. Furthermore, two or more supplements per week were taken by 44.2% and 38.7% of the colorectal cancer patients at diagnosis and two years post-diagnosis compared to 28.5% of the patients six months post-diagnosis.

Consistency of dietary supplement use

Table 6.3 shows that 70 (43.8%) of the 160 colorectal cancer patients were inconsistent users, while 34 (21.3%) were consistent users, and 56 (35.0%) were consistent nonusers. Among patients who were user at colorectal cancer diagnosis (n=61), 55.7% kept using supplements six months and two years post-diagnosis, 11.5% interrupted use only at six months post-diagnosis, 19.7% stopped using supplements two years after the diagnosis, and 13,1% completely stopped use after diagnosis. Among the patients who were nonuser at colorectal cancer diagnosis (n=99), 56.6% also remained nonuser after diagnosis, whereas 22.2% initiated use six months post-diagnosis only, 8.1% started taking supplements two years post-diagnosis only, and 13.1% used supplements six months and two years post-diagnosis.

Among the inconsistent users (n=70), 52.9% took more supplements, 28.6% used less supplements, and 18.6% took the same number of supplements six months post-diagnosis when compared to diagnosis (data not shown). Among the consistent users (n=34), 8.8% used more supplements, 14.7% took less supplements, and around 75% did not change

Table 6.2 Dietary supplement use at colorectal cancer diagnosis, six months and two years post-diagnosis in a prospective cohort study among colorectal cancer patients

Characteristic	Total population (n=160)	
	n	(%)
Current use at colorectal cancer diagnosis of any supplement once a week during the last month		
At colorectal cancer diagnosis	61	(38.1)
Six months post-diagnosis	81	(50.6)
Two years post-diagnosis	62	(38.8)

	At colorectal cancer diagnosis		Six months post-diagnosis		Two years post-diagnosis	
	Users[¥] (n=61)		Users[¥] (n=81)		Users[¥] (n=62)	
	n	(%)	n	(%)	n	(%)
Dietary supplement use						
Type of supplement						
Multivitamin/-mineral*	33	(54.1)	39	(48.2)	36	(58.1)
Vitamin C	6	(9.8)	9	(11.1)	6	(9.7)
Vitamin D	5	(8.2)	9	(11.1)	6	(9.7)
Folic acid	6	(9.8)	6	(7.4)	4	(6.5)
Calcium	8	(13.1)	7	(8.6)	3	(4.8)
Magnesium	7	(11.5)	18	(22.2)	6	(9.7)
Iron	9	(14.8)	13	(16.1)	4	(6.5)
Fish oil	11	(18.0)	7	(8.6)	10	(16.1)
Herbal & specialty supplements[§]	18	(29.5)	13	(16.0)	26	(41.9)
Other	10	(16.4)	8	(9.9)	8	(12.9)

Table 6.2 continues on next page

Table 6.2 *Continued*

	At colorectal cancer diagnosis		Six months post-diagnosis		Two years post-diagnosis	
	Users[¥] (n=61)		Users[¥] (n=81)		Users[¥] (n=62)	
	n	(%)	n	(%)	n	(%)
Amount of supplements taken at least 1x per week during the last month						
1 supplement	34	(55.6)	58	(71.6)	38	(61.3)
2 supplements	16	(26.2)	13	(16.1)	11	(17.7)
≥3 supplements	11	(18.0)	10	(12.4)	13	(21.0)

[¥] Use of a dietary supplement at least once per week during the last month.

* Multivitamin/minerals supplements or other supplements include a combination of at least two vitamins and/or minerals (e.g. vitamin B-complex, combination of antioxidants, combination of vitamin A/D, combination of calcium/magnesium/zinc, other combinations).

[§] Herbal & specialty supplements include supplemental garlic, brewer's yeast, lecithin, glucosamine, coenzyme Q10, Echinacea, ginseng, methylsulfonyl-methane, and fibre.

Table 6.3 Consistency of dietary supplement use in a prospective cohort study among colorectal cancer patients

	Total population	
Change in supplement use	n	(%)
Consistency of supplement use (n=160)¥		
Consistent users	34	(21.3)
Inconsistent users	70	(43.8)
Consistent nonusers	56	(35.0)
Supplement use at colorectal cancer diagnosis (n=61)*		
Subjects who kept using supplements at diagnosis, six months and two years post-diagnosis	34	(55.7)
Subjects with interrupted use six months post-diagnosis only	7	(11.5)
Subjects with interrupted use two years post-diagnosis only	12	(19.7)
Subjects who stopped using supplements six months and two years post-diagnosis	8	(13.1)
No supplement use at colorectal cancer diagnosis (n=99)§		
Subjects who kept not using supplements at diagnosis, six months and two years post-diagnosis	56	(56.6)
Subjects with interrupted non use six months post-diagnosis only	22	(22.2)
Subjects with interrupted non use two years post-diagnosis only	8	(8.1)
Subjects who started supplement use six months and two years post-diagnosis	13	(13.1)

¥ Consistent nonusers were defined as subjects reporting no regular supplement use at diagnosis, six months and two years post-diagnosis; Inconsistent users were defined as subjects reporting differences in regular supplement use at diagnosis, six months or two years post-diagnosis; Consistent users were defined as subjects reporting regular supplement use at diagnosis, six months and two years post-diagnosis.
* Use of a dietary supplement at least once per week during the last month.
§ No use during the last month.

their intake with regard to the number of supplements six month post-diagnosis compared to diagnosis. More than half of the inconsistent users increased their use between diagnosis and six months post-diagnosis, but thereafter, between six months and two years post-diagnosis around 35% decreased their use. Among the consistent users, 55.9% did not change their intake six months and two years post-diagnosis (data not shown).

Comparison between inconsistent users with consistent users and nonusers

Inconsistent users were more often women compared with consistent users and consistent nonusers (**Table 6.4**). Furthermore, consistent and inconsistent users were more often higher educated than consistent nonusers. Colorectal cancer patients with stage III of the disease were more often inconsistent users (38.6%) compared to those with stage I and II disease. Also, patients who were treated with surgery only, more often consistently used

Table 6.4 Sociodemographic and disease related characteristics, lifestyle and dietary factors of consistent nonusers, inconsistent and consistent users at diagnosis, six months and two years post-diagnosis in a prospective cohort study of colorectal cancer patients

Characteristic	Consistent nonusers[¥] (n=56)		Inconsistent users* (n=70)		Consistent users[§] (n=34)	
Sociodemographic characteristics						
Age at study entry [mean (SD)]	65.3	(9.7)	64.4	(10.1)	66.8	(12.0)
Women [n (%)]	17	(30.4)	33	(47.1)	15	(44.1)
High educational level [n (%)]	10	(17.9)	20	(29.0)	12	(35.3)
Family history of cancer [n (%)][¶]	40	(80.0)	51	(77.3)	26	(89.7)
Disease related characteristics						
Stage of the disease [n (%)][¶]						
Stage I	18	(32.1)	15	(21.4)	11	(32.4)
Stage II	16	(28.6)	22	(31.4)	16	(47.1)
Stage III	16	(28.6)	27	(38.6)	3	(8.8)
Stage IV	2	(3.6)	0		2	(5.9)
Cancer therapy [n (%)]						
Surgery only	24	(42.9)	25	(35.7)	24	(70.6)
Surgery plus radiotherapy	8	(14.3)	8	(11.4)	4	(11.8)
Surgery plus chemotherapy	14	(25.0)	26	(37.1)	2	(5.9)
Surgery plus chemoradiation	8	(14.3)	9	(12.9)	3	(8.8)
Surgery plus radiotherapy plus chemotherapy	2	(3.6)	1	(1.4)	1	(2.9)
Lifestyle and dietary factors[#]						
Body mass index [kg/m^2, mean (SD)]	25.9	(3.7)	26.0	(3.7)	25.2	(4.0)
Current smokers [n (%)][¶]	10	(17.9)	5	(7.3)	5	(14.7)
NSAID use ≥1 time/month [Yes, n (%)]	3	(5.4)	10	(14.3)	3	(8.8)
Physical active for ≥30 minutes per day [n (%)][¶]	41	(74.6)	49	(71.0)	27	(79.4)
Fruit intake [pieces/day, median (IQR)][¶]	0.7	(0.4–1.9)	1.3	(0.6–1.9)	1.9	(0.6–1.9)
Vegetables intake [g/day, median (IQR)][¶]	104.2	(64.3–147.6)	103.0	(82.4–132.0)	115.0	(79.8–144)
Red and processed meat intake [g/day, median (IQR)][¶]	68.8	(50.5–81.4)	52.0	(27.7–74.4)	56.6	(25.6–74.2)
Alcohol intake [glasses/day, median (IQR)][¶]	0.7	(0–2.1)	0.4	(0–1.5)	0.7	(0.1–1.4)

[¥] Consistent nonusers were defined as subjects reporting no regular supplement use at diagnosis, six months and two years post-diagnosis.

* Inconsistent users were defined as subjects reporting differences in regular supplement use at diagnosis, six months or two years post-diagnosis.

[§] Consistent users were defined as subjects reporting regular supplement use at diagnosis, six months and two years post-diagnosis.

[¶] <5% missing.

[#] Lifestyle and dietary factors at colorectal cancer diagnosis.

dietary supplements (70.6%) compared to other cancer therapies. No other remarkable differences were present between inconsistent users and consistent users and nonusers.

DISCUSSION

This study is the first prospective cohort study among colorectal cancer patients in Europe which repetitively assessed dietary supplement use over time after diagnosis. Our results showed that dietary supplement use was common at colorectal cancer diagnosis (38.1%), six months (50.6%) and two years post-diagnosis (38.8%). Nevertheless, supplement use changed over time in 43.8% of the patients.

Our study showed that there was a great variability over time in dietary supplement use after colorectal cancer diagnosis. Despite the high prevalence of use at diagnosis (38.1%), only 21.3% of the total population of colorectal cancer patients were consistent users. Among stage III colorectal cancer patients in our study, inconsistent use (58.7%) was higher compared to a study among stage III colon cancer patients in the United States in which 34% of the patients reported inconsistent use. [34] This difference could be explained by the fact that the consistency of dietary supplement use in that study was only reported during adjuvant chemotherapy and six months thereafter, while no information about use was available at diagnosis and several years post-diagnosis. Comparable with other studies among colon cancer patients in the United States, [25,27] our findings showed that more patients took dietary supplements directly after colorectal cancer diagnosis and six months post-diagnosis, but a substantial proportion of these patients already have stopped their use two years post-diagnosis. According to our results, it seems that colorectal cancer patients especially initiated use six months post-diagnosis (22.2%), i.e. mostly during cancer therapy, which was similar to another Dutch study among a heterogeneous group of cancer patients (16%). [22] This also indicates that dietary supplement use is not a constant behavior after colorectal cancer diagnosis.

On advice from their clinician, colorectal cancer patients might start using supplements when they have a deficient blood level of vitamins or minerals, or they quit supplemental intakes when the levels in the blood are normalized, which could explain the temporary increases regarding use of supplemental iron and magnesium during cancer therapy in our study. In addition, our results showed that colorectal cancer patients took more vitamin D, but less vitamin A, vitamin C, vitamin E, folic acid, fish oil, and herbal and specialty supplements during

cancer therapy. It has been suggested that intake of dietary supplements during cancer therapy might be harmful since supplements may possibly interact with conventional cancer treatments. [2-11,43,44] Some investigators suggested that use of supplemental antioxidants and folic acid could interfere with the effectiveness of chemotherapy or radiotherapy and support tumor growth, [45-47] while others argue that those supplements enhance the effects of cytotoxic therapy. [46,48-52] Although effects of supplementation of vitamin D during cancer therapy are largely unknown yet, some studies suggested beneficial effects against cancer cells, such as inhibition of cancer cell growth by antiproliferation and prodifferentiation, [10,11] enhanced response rates to chemotherapeutic drugs, and reduced side effects by reductions in the concentrations of conventional anticancer drugs. [7,44] An animal study of rodents indicated that fish oil supplementation might cause retarded growth of tumor cells, while, on the contrary, oxidative damage enhanced lipid peroxidation to toxic levels in mammary tumors. [8] Furthermore, the herbal supplement St. John's wort, which is often used to manage depression, [53] inhibits the effectiveness of the chemotherapy agent irinotecan. [54,55] Firm conclusions cannot be drawn, because evidence about the safety and benefits of supplements with conventional cancer treatments is limited. [56] However, before such possible interactions can be studied it is important to obtain detailed and repeated information on dietary supplement use shortly after diagnosis and during and after cancer therapy.

The main strength of the current study was that dietary supplement use is repeatedly assessed over time which enabled us to explore the consistency of use. Colorectal cancer patients might alter their use directly after diagnosis and during cancer therapy in the belief that supplements might prevent recurrence or could be beneficial for the treatment of their disease. [32] In most studies, it was not possible to report on the consistency of use since use was not repetitively assessed, but only at one point in time, i.e. before colorectal cancer diagnosis, [28] during cancer therapy, [22,26,27] or several years post-diagnosis. [21,57-59] If supplement use is only assessed once, findings could be biased due to misclassification of dietary supplement use. Furthermore, two studies reported on use before colorectal cancer diagnosis compared with use several years post-diagnosis, [25,27] but they did not report on use during cancer therapy. Again, before associations between dietary supplement use and recurrence or survival in colorectal cancer patients can be examined, it is of importance that studies repetitively assess use in order to get more insight into the variability of use over time.

Two considerations about our study should be mentioned. First, colorectal cancer patients in any stage of the disease were eligible for our study, which means that a heterogeneous

group of patients was included. The distribution of patients with stage I, II, or III of the disease in our study corresponds to the distribution of colorectal cancer cases as reported by the Dutch Cancer Registry [60] and as also reported in a population-based cohort in the Netherlands. [61] However, use of dietary supplements might especially be common in stage IV colorectal cancer patients, [31,32] in order to improve their wellbeing and quality of life. Since stage IV patients are underrepresented in our study due to medical and ethical reasons, our findings might only be generalizable to colorectal cancer patients who underwent curative treatment for disease stage I, II, or III.

The second consideration concerns the possibility of misclassification of dietary supplement use since use was assessed by self-report of the participants. However, several studies showed that self-reported use of dietary supplements is reliable to measure the actual intake. [62-64] We were able to expand our knowledge on use of supplements among colorectal cancer patients by having detailed information about use with regard to type of supplement, frequency of intake, amount of intake, dosage and duration. In preparation for the current study, we conducted a pilot study among 148 healthy men and women in the general population comparing dietary supplement use elicited by our questionnaire to supplement use obtained by three 24-hour recalls. Overall, the questionnaire demonstrated Spearman correlation coefficients ranging from 0.35–0.75 for most of the supplements, and kappa's for 'ever use' versus 'never use' of dietary supplements between the questionnaire and the 24-hour recalls ranged from 0.53–0.90. We therefore assume that self-reported dietary supplement use is a reliable indicator for the actual intake, and the potential of misclassification of dietary supplement use in our study is limited.

The final consideration is that we were not able to explore whether consistent users used the same or different types of dietary supplements directly after colorectal cancer diagnosis, and six months and two years post-diagnosis due to the low numbers of patients in our study.

In conclusion, our results showed that dietary supplement use among colorectal cancer patients is common, but use varies over time after colorectal cancer diagnosis. Therefore, multiple assessments of dietary supplement use over time are highly recommended in order to get more insight into the variability of use. These results also suggest that studies among colorectal cancer patients investigating the association between dietary supplement use and recurrence and survival should obtain repeated information on dietary supplement use in order to get a good estimate of dietary supplement use.

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Chapter 7

General discussion

This thesis addressed the associations between dietary supplement use and colorectal tumor risk and recurrence in the general population and in high-risk populations for colorectal cancer, and explored the consistency of dietary supplement use over time in newly diagnosed colorectal cancer patients. For this purpose, data from three prospective cohort studies among individuals with a history of sporadic colorectal adenomas, individuals with Lynch syndrome, and individuals with colorectal cancer were used. In addition, the current literature on dietary supplement use and colorectal cancer risk in the general population was systematically reviewed and meta-analysed.

MAIN FINDINGS

An overview of the studies and the main findings of this thesis are pointed out in **Table 7.1**. Our results do not indicate a preventive or harmful role for dietary supplement use in colorectal tumor etiology and recurrence in the general population and in high-risk populations for colorectal cancer. Also, dietary supplement use appeared to be inconsistent over time after colorectal cancer diagnosis, and use should be assessed at more than one time point. This paragraph discusses the main findings of this thesis as compared to the existing literature, if any. Furthermore, possible explanations for the discrepancies between our findings and results from others are given.

According to the systematic literature review with meta-analyses in **chapter 2**, inverse associations between multivitamin use, calcium supplement use and colorectal cancer risk were found, but inconsistent associations were shown for use of other supplements and risk of colorectal cancer. Our findings for use of multivitamins, supplemental vitamin A, vitamin C, vitamin E, and calcium on colorectal cancer risk were in line with pooling studies which included available primary data of prospective cohorts only. [1,2] Different from our results, another pooled analysis of 13 cohort studies showed a non-statistically significant inverse association for supplemental intakes of folate with colon cancer risk. [3] However, except for multivitamin use, the pooled data were based on data from foods and supplements combined, whereas our study focused on supplemental intakes only. Expert guidelines from the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) did not recommend use of dietary supplements for cancer prevention. [4] However, this conclusion from the WCRF/AICR is mainly based on large randomized trials on cancer outcomes other than colorectal cancer, or colorectal cancer as a secondary outcome. It is still unknown whether those recommendations are also applicable for patients at risk for

Table 7.1 Overview of the studies and main findings presented in this thesis

Chapter	Type of study	Study population	Exposure	Outcome	Main findings
2	Systematic review and meta-analyses of observational studies	General population (total N=2,493,878; cases n=23,501)	Dietary supplement use	CRC risk	Inverse association between multivitamin use (RR=0.92; 95% CI 0.87–0.97), calcium supplement use (RR=0.86; 95% CI 0.79–0.95) and CRC risk. Inconsistent associations for use of other supplements and CRC risk.
3	Prospective cohort - POLIEP follow-up study -	Individuals with a history of sporadic CRA (n=565)	Dietary supplement use	Recurrence of CRA	No association between dietary supplement use and total CRA recurrence (HR=1.03; 95% CI 0.79–1.34) or recurrent advanced adenomas (HR=1.59; 95% CI 0.88–2.87).
4	Prospective cohort - GeoLynch cohort study -	Individuals with Lynch syndrome (n=470)	Dietary supplement use	CRA risk	No association between any dietary supplement use (HR=1.18; 95% CI 0.80–1.73), multivitamin use (HR=1.15; 95% CI 0.72–1.84), and supplemental vitamin C (HR=1.57; 95% CI 0.93–2.63), calcium (HR=0.69; 95% CI 0.25–1.92), and fish oil (HR=1.60; 95% CI 0.79–3.23) and CRA.
5	Prospective cohort - COLON study -	CRC patients	N.A.[¥]	N.A.[¥]	N.A.[¥]
6	Prospective cohort - COLON study -	CRC patients (n=160)	Consistency of dietary supplement use	-	Dietary supplement use among CRC patients is common at diagnosis (~40%), during cancer therapy (~40%), and 2 years post-diagnosis (~50%), but use appears to be inconsistent over time after diagnosis: 43.8% were inconsistent users.

Abbreviations: CRC=colorectal cancer; CRA=colorectal adenoma; N.A.=Not applicable.
[¥] Not applicable, since this chapter describes the design of the COLON study.

colorectal cancer as no conclusions about the evidence on dietary supplement use and colorectal cancer risk could be made yet due to limited randomized trials. Thus, our study is the first systematic literature review with meta-analyses of prospective cohort studies which provides an extensive overview about the associations between dietary supplement use and colorectal cancer risk.

Furthermore, no association between dietary supplement use and total colorectal adenoma recurrence nor with recurrent advanced adenomas in a population of individuals with a history of colorectal adenomas was observed (**chapter 3**). No other prospective cohort study explored associations between use of individual dietary supplements and colorectal adenoma recurrence yet, whereas associations for use of some individual supplements and recurrence of colorectal adenomas have been investigated by several randomized controlled trials, [5-13] two prospective observational analyses within two randomized controlled trials, [14,15] and one case-control study. [16] Our findings for use of individual supplements are different compared to the results of those studies: no associations for use of multivitamins and supplemental calcium including vitamin D and colorectal adenoma recurrence were found, whereas in other studies inverse associations were reported. [6,9,14-17] Furthermore, although a small group of users of supplemental vitamin B (including folic acid) was present in our study, a statistically significantly increased risk of supplemental vitamin B intake and colorectal adenoma recurrence was found, while other studies showed inconsistent associations. [7,10,11,13] The discrepancies between our findings in the prospective cohort study and the randomized controlled trials could be explained by the fact that in those trials the intake, dosage, and the composition of the supplements were prescribed and comprised fixed calendar packages, whereas in our prospective cohort study the habitual intake of supplements has been assessed whereby intake, dosage, and composition of the supplements can vary substantially between individuals during the year.

Also, the prospective cohort study among individuals with Lynch syndrome did not show statistically significant associations between dietary supplement use and colorectal adenoma risk (**chapter 4**). To the very best of our knowledge, the role of dietary supplement use in colorectal adenoma development in a Lynch syndrome population is still unclear as no other study evaluated this association so far.

Finally, the prospective cohort study among colorectal cancer patients, of which the design of the study was described in **chapter 5**, demonstrated that dietary supplement use among colorectal cancer patients is common, but use varied over time after diagnosis (**chapter 6**).

Only one other study explored the consistency of multivitamin use in prospective observational analyses among stage III colon cancer patients receiving chemotherapy who were originally enrolled in the Cancer and Leukemia Group B (CALGB) trial in the United States. [18] That study among stage III colon cancer patients showed that, among 799 patients with available data on multivitamin use during and six months after adjuvant chemotherapy, 34% were inconsistent users, 40% were consistent users, and 26% were consistent nonusers. [18] These percentages were different from the proportions reported in our study, i.e. 44% were inconsistent users, while 21% were consistent users and 35% were consistent nonusers, and could be due to the following explanations: In general, dietary supplement use is higher in the United states than in Europe. Also, as compared to the CALGB trial, our study included a more diverse group of patients, i.e. all disease stages and cancer therapies, and had a longer follow up. Furthermore, our study explored whether supplement use is constant over a longer period of time by assessing use at diagnosis of colorectal cancer, during cancer therapy, and two years post-diagnosis, while the CALGB trial only evaluated the consistency of use during and shortly after chemotherapy [18]. As our study included a heterogeneous group of colorectal cancer patients compared to only stage III colon cancer patients receiving chemotherapy in the CALGB trial, our results might be generalizable to other colorectal cancer patients with different disease stages and cancer therapies.

METHODOLOGICAL CONSIDERATIONS

Most of the epidemiological issues of the studies presented in this thesis have been discussed in previous chapters. Nevertheless, before the research question of the thesis can be answered, relevant methodological considerations of the thesis as a whole should be addressed. This paragraph discriminates between issues that may affect the internal and external validity of the observed associations. An issue that is neither part of the internal nor the external validity is causation, and will be pointed out below.

On the basis of the currently conducted observational studies, no statement on causation with regard to the association between dietary supplement use and colorectal tumor risk and recurrence can be made, which is a typical problem for observational studies. We should be aware of the fact that reverse causation could be present. In the POLIEP follow-up study and in the GeoLynch cohort study, a history of colorectal adenomas could have influenced dietary supplement use of those individuals. To investigate whether reverse

causation could have affected our results, we conducted sensitivity analyses in the POLIEP follow-up study, i.e. a cohort among persons with a history of sporadic colorectal adenomas, by comparing persons who all had an adenoma recurrence at the recruitment endoscopy with those without an adenoma recurrence at the recruitment endoscopy. These analyses did not markedly change the association between dietary supplement use and colorectal adenoma recurrence. Furthermore, in the GeoLynch cohort study, sensitivity analyses for prevalent and incident cases of colorectal adenomas showed minor differences in associations between dietary supplement use and colorectal adenoma risk in individuals with Lynch syndrome. The results from the sensitivity analyses and the fact that colorectal adenomas are often asymptomatic indicate that it is not likely that reverse causation was responsible for our findings.

Internal validity

This section about the internal validity consists of three parts, including methodological issues of dietary supplement use assessment, considerations regarding the endpoints, and confounding factors. Each part will be separately discussed below.

I. Challenges in dietary supplement use assessment

As also described in **chapters 2, 3, and 4**, a good comparison and interpretation of associations between dietary supplement use and colorectal tumor risk or recurrence between studies is difficult. Due to the explosion in the types of supplements available and various combinations of vitamin, mineral, and herbal products in the last decades, differences in definition and categorization of dietary supplement use, dosage and composition of the supplement, intake, frequency of use, and variations in use within and between countries, are present. As a consequence, associations between dietary supplement use and colorectal tumor risk or recurrence could be over- or underestimated as it is not always possible to anticipate on the most recent developments in assessment of dietary supplement use. Also, the lack of associations between any use of all dietary supplements together and colorectal tumor risk or recurrence in this thesis could be a result of neutralization of individual effects of each nutrient supplement.

In this thesis, dietary supplement use was assessed with self-administered questionnaires as in many epidemiological studies. [19,20] In the POLIEP follow-up study and the GeoLynch cohort study specifically, those brief and simple questionnaires, which seem to be adequate

for assessment of supplements, [19,20] contained questions about dietary supplement use in general, and about use, frequency and amount of intake for the most commonly used dietary supplements (e.g. multivitamins, B-complex, combination of antioxidants, calcium and/or vitamin D supplements). However, detailed information on duration of use, dosage of intake, and on specific types or mixtures of supplements that are commonly used, e.g. magnesium, iron, combination of calcium/magnesium/zinc, or herbal and specialty supplements was missing in those questionnaires. As a result, in the POLIEP follow-up study and in the GeoLynch cohort study, we were not able to evaluate associations with use of specific dietary supplements in detail. Since dietary supplement use has increased and the types and combinations of supplements have exploded in the recent past decades worldwide, [21,22] those brief and simple questionnaires could not adequately capture supplement intake anymore.

In order to anticipate on these developments of dietary supplement use for our new prospective cohort study among colorectal cancer patients, i.e. the COLON study, we developed a questionnaire which assesses use extensively. This study aims to investigate the association between dietary supplement use and colorectal tumor recurrence and survival. The detailed questionnaire thoroughly asks about use during the last year (i.e. type of supplement, the months the supplements were taken, duration of use), and about current use (frequency of intake, amount of intake, unit of intake, dosage, brand name, and ingredients of the supplement). In addition, this newly developed questionnaire on dietary supplement use contains questions on use of specific types of supplements, i.e. multivitamin/minerals supplements and other combinations not classified as multivitamins/minerals (e.g. vitamin B-complex, combinations of antioxidants, combination of vitamin A/D, combinations of calcium/magnesium/zinc, other combinations), and supplemental vitamin A, folic acid, vitamin B12, vitamin C, vitamin D, vitamin E, calcium, magnesium, zinc, iron, selenium, chrome, fish oil, and herbal and specialty supplements. Still, during the course of this thesis we encountered several challenges in assessing and interpreting dietary supplement use, which have been described below.

Misclassification of dietary supplement use

The observed associations in this thesis may be prone to misclassification of dietary supplement use. It is important to consider to what extent the associations were influenced by these errors, since the internal validity might be affected. Below, two issues on potential misclassification of dietary supplement use, as assessed in the studies in this thesis, will be discussed.

Assessment of dietary supplement use by self-report

Dietary supplement use was assessed by self-report of the participants in the studies described in this thesis. However, self-reported dietary supplement use by questionnaires is prone to underreporting, [23] whereby the association between dietary supplement use and colorectal tumor risk might be underestimated. However, we do not expect that our associations in the POLIEP study and GeoLynch cohort study were influenced by this bias as prior studies showed that assessment of dietary supplement use by self-administered questionnaires is reliable. [19,24] Moreover, dietary supplement use was recorded before any knowledge of colorectal adenoma recurrence among individuals with a history of colorectal adenomas or colorectal tumor risk among individuals with Lynch syndrome was present, and thereby reducing the likelihood of reporting biases and differential misclassification.

Furthermore, we assume that bias by self-reported dietary supplement use is also limited in the COLON study. To evaluate this, we conducted a study among 148 healthy men (n=57) and women (n=91) in the general population comparing dietary supplement use assessed by this questionnaire to use obtained by three 24-hour recalls shortly after the questionnaire. Overall, the detailed questionnaire in the COLON study provided comparable assessments of the most commonly used dietary supplements as Spearman correlation coefficients between questionnaire and 24-hour recalls ranged from 0.35–0.75, and kappa's for 'ever use' versus 'never use' were 0.53–0.90 (**Table 7.2**). Thus, for the findings in this thesis, we assume that self-reported dietary supplement use is a reliable indicator for the actual intake, and therefore the potential of misclassification of dietary supplement use is limited.

Table 7.2 Interpretation of the Spearman correlation coefficient [25] and Cohen's kappa [26]

Spearman correlation coefficient	No	Weak		Moderate	Strong	(Almost) perfect
	0.00	0.30		0.50	0.70	1.00
Kappa	Poor	Slight	Fair	Moderate	Substantial	(Almost) perfect
	0.00	0.20	0.40	0.60	0.80	1.00

Inconsistency of dietary supplement use over time

Although dietary supplement use may be an unstable behaviour in the general population, [27,28] little is known about the consistency of use over time. The EPIC study concluded that supplement use is fairly unstable in free-living individuals, but individuals with a favourable lifestyle and healthier diet are more likely to show consistent supplementation. [27]

Furthermore, a large cohort of French women from the general population reported that 26.7% of the users became nonusers while 21.8% of the nonusers became users after a 2-year follow-up. [28] Our study among colorectal cancer patients (**chapter 6**) showed that the prevalence of supplement use was ~40% at diagnosis and two years post-diagnosis, and around 50% during cancer therapy, but use appeared to be inconsistent over time after diagnosis of colorectal cancer. Also, for our other cohorts among individuals with a history of sporadic colorectal adenomas (**chapter 3**) and among individuals with Lynch syndrome (**chapter 4**), supplement use might be unstable over time as those individuals might change their use during the course of life based on their health status and risk. In those studies, we did not evaluate the stability of dietary supplement use over time, but no specific recommendations exist for meaningful lifestyle changes after diagnosis of a colorectal adenoma. [29,30] We therefore assume that intake of dietary supplements by colorectal adenoma patients is relatively constant during the follow-up period in the POLIEP follow-up study and in the GeoLynch cohort study.

Obviously, it is not possible to evaluate consistency of dietary supplement use with only one assessment of use in a specific population. An appropriate way to deal with the potential instability of use is to assess dietary supplement use repetitively over time, as already applied in the COLON study. Repeated measurements were recommended as an effective method of reducing the within-subject variation and, thereby, decreasing the measurement error compared with the use of a single assessment. [31,32] For data-analyses of repeated measures of dietary supplement use over time, repeated-measures ANOVA is widely used for the analysis of repeated-measures data, such as dietary supplement use. Furthermore, mixed-effects models use all available data, and can properly account for correlation between repeated measurements on the same subject. [31,32] In the POLIEP follow-up study, the GeoLynch cohort study, and in nearly all of the prospective cohort studies evaluated in our systematic literature review we did not have repeated information on dietary supplement use, and this lack of information could therefore have implications for the observed associations in this thesis.

II. High-risk populations of colorectal tumors: misclassification of the outcome

Three study populations have been described in this thesis, namely individuals with a history of sporadic colorectal adenomas, individuals with Lynch syndrome, and individuals with colorectal cancer. This section reports several considerations regarding misclassification of those endpoints.

Surveillance and screening

In the observed associations described in this thesis, misclassification of the outcomes could be present. Individuals with a history of sporadic colorectal adenomas (POLIEP follow-up study) and individuals with Lynch syndrome who have a high familial risk of developing colorectal adenomas and colorectal cancer (GeoLynch cohort study) are under constant surveillance and screening for colorectal adenomas according to the Dutch guidelines in order to prevent colorectal cancer. [33,34] Generally, the presence of a colorectal adenoma causes no symptoms [35] and can only be detected during a colonoscopy. Individuals with a history of sporadic colorectal adenomas are advised to have a follow-up colonoscopy 6 years after the previous colonoscopy when no or less than 3 adenomas are present. When 3 or more adenomas are detected in those individuals, a follow-up colonoscopy is recommended after 3 years. [34] However, due to a variety of reasons, such as being more health-conscious after colorectal adenoma diagnosis, differences in time intervals between the colonoscopies could be present. As a consequence, the possibility of missed adenomas could be present. Unfortunately, it was not possible to influence the procedures regarding follow-up colonoscopies as this was part of the routine of the hospitals. Therefore, we accounted for various time intervals between recurrent events in the POLIEP follow-up study by using stratified cox proportional hazard models for counting processes as was described in **chapter 3** of this thesis.

Surveillance and screening practices are more standardized in individuals with Lynch syndrome. Those individuals are highly recommended to undergo a full colonoscopy at an interval of two years [33] leading to less variation in time between the colonoscopies, and less missed adenomas compared to individuals in the POLIEP follow-up study. Therefore, it could be that more precise associations were found in the GeoLynch cohort study compared to the POLIEP follow-up study. The potential of misclassification of the outcome is small in the COLON study as individuals were diagnosed with colorectal cancer by their clinician, and resections of the tumor were histologically confirmed by the pathology lab.

Missed medical information

Information on the endpoints in the POLIEP follow-up study, the GeoLynch cohort study, and the COLON study, i.e. colorectal adenoma recurrence, colorectal adenoma risk, and colorectal cancer respectively, was gathered via medical records from hospital registries which were seen as the golden standard. For some participants under study, retrieval of medical information was not possible as participants could have moved or decided not to

further participate in the study. In total, from 91% of the patients in the POLIEP follow-up study and from 94% of the patients in the GeoLynch cohort study, medical information was complete. In addition, we were able to collect medical information from 83% and 94% of the participants in the COLON study six months post-diagnosis and two years post-diagnosis respectively. An underlying reason for not participating into the study anymore could be the potential high physical and mental burden of the disease in combination with filling out extensive, detailed and comprehensive questionnaires and blood draws. For the POLIEP follow-up study and the GeoLynch cohort study specifically, ending the surveillance for colorectal adenomas based on the current guidelines for screening colonoscopies could also play a role. [33,34] Our findings might probably not be influenced by this lack of information, since it is not plausible that this lack will be associated with dietary supplement use.

For the GeoLynch cohort study, identification of Lynch syndrome carriers took place via the tumor registry of the Netherlands Foundation for the Detection of Hereditary Tumors (NFDHT), and outcome information from medical records via medical specialists was obtained. The NFDHT repeatedly requests information from medical records of high risk families of a hereditary tumor to their medical specialist in order to coordinate surveillance and screening. However, information could be delayed by administrative matters. Therefore, it could be that not all relevant information was collected through this extra step whereby adenomas might have been missed. Nevertheless, this missed information has not biased our findings as this lack might not be associated with dietary supplement use in individuals with Lynch syndrome.

Histologically confirmed cases

Information on colorectal tumor cases in the POLIEP follow-up study, the GeoLynch cohort study, the COLON study, and the prospective cohort studies included in the systematic literature review was obtained by self-report, medical records, and through linkage to national cancer registries, pathology registries, or population registries. Most of the removed lesions of participants in the POLIEP follow-up study, GeoLynch cohort study, and COLON study were sent out to the pathology lab in order to ascertain the histology of the lesion. However, in some hospitals in the POLIEP follow-up study, not all lesions were histologically confirmed by the pathology lab, but were probably based on the endoscopists' own judgement on the removed lesion. In this way, a colorectal adenoma could have been missed, and misclassification of the outcome could be present due to

the fact that, for example, hyperplastic polyps or small nonadvanced polyps might be adenomas histologically, but were not classified as such. Although misclassification of the outcome cannot be totally avoided in the POLIEP follow-up study, no remarkable changes of the effect estimates were observed when adenoma type was considered as a potential confounding factor.

III. Confounding

Potential bias by confounding is common in observational research, and can easily bias the association of interest. Studies described in this thesis and several other studies have shown that dietary supplement use is more prevalent among women than among men, and use increases with age in both men and women. [27,36,37] Furthermore, users tend to be better educated, have somewhat healthier dietary patterns, exercise regularly, maintain a healthy weight, and smoke less compared to nonusers. [27,36,37] Based on these factors, users appear to be a very specific health-conscious group who adopt various dietary and lifestyle habits assumed to contribute to a healthy lifestyle. These differences in demographic, lifestyle, and dietary factors between users and nonusers could have affected our associations described in this thesis. Nevertheless, we were aware of various lifestyle and dietary factors as potential confounders, and potential confounding factors, including age, sex, educational level, and dietary, lifestyle, and disease-related factors were evaluated. However, residual confounding can never be completely ruled out because of unmeasured or inaccurate measured potential confounding variables.

One confounder, i.e. educational level, should warrant further attention. Educational level is, rather than income and occupation, [38] the most commonly used marker of social economic status in epidemiological studies, [39] and may be the strongest predictor of good health and a variety of lifestyles. [38] Adjustment for educational level and lifestyle factors at the same time might therefore lead to overadjustment of lifestyle factors. Besides adjustments for age, sex, and number of colonoscopies in our analyses in the POLIEP follow-up study, additional adjustments were made for educational level, while this was not the case in the analyses of the GeoLynch cohort study. However, in the POLIEP follow-up study we adjusted for educational level only and not for any other lifestyle factor. Unfortunately, some studies in the systematic literature review adjusted for educational level and several lifestyle factors simultaneously, which could have led to biased estimates of the effect measure.

External validity

If the internal validity is considered to be high as discussed in the previous section, it is of next importance to evaluate the external validity of the study results. In this section, the heterogeneity of the study populations, and the representativeness of the study results will be pointed out.

I. Heterogeneity of the study populations

Heterogeneity of the populations under study with regard to disease stage, cancer therapy, and having a history of former adenomas before the recruitment endoscopy, could have had implications for the observed associations in this thesis. For example, heterogeneity should be taken into account in the interpretation of our results in the COLON study (**chapter 5**), as those patients with colorectal cancer had different disease stages and different cancer therapies. Furthermore, both in the POLIEP follow-up study (**chapter 3**) and in the GeoLynch cohort study (**chapter 4**), former adenomas before the recruitment endoscopy, which are an important risk factor for developing colorectal adenomas, [40] were present. Hypothetically, it is plausible that different determinants could attribute to adenoma development when persons who had their first adenoma at the recruitment endoscopy ('incident' cases) were compared to those with a history of adenomas preceding the recruitment endoscopy ('prevalent' cases). However, most adenomas arise via the adenoma-carcinoma sequence presuming common risk factors. [41,42] Sensitivity analyses did not show differences in associations between dietary supplement use and colorectal adenoma recurrence in persons with or without former adenomas before the recruitment endoscopy (POLIEP follow-up study), while in individuals with Lynch syndrome a small borderline statistically significantly increased risk for colorectal adenomas was observed among those who had former adenomas probably due to the high familial risk. Nonetheless, due to the relatively small populations in this thesis, no firm conclusions considering differences between individuals with and without former adenomas can be drawn yet.

II. Representativeness of the cohort studies

The representativeness of the systematic literature review with meta-analyses of prospective cohort studies, the POLIEP follow-up study, the GeoLynch cohort study, and the COLON study examined in this thesis is important for the translation of the findings

to populations were the study participants are coming from. This section discusses the extrapolation of our findings to these target populations.

Systematic literature review with meta-analyses

Our findings in the systematic literature review, including the meta-analyses, are representative for individuals at risk for colorectal cancer in the general population as many different and large study populations were prospectively studied. However, it should be noted that, although this issue is unavoidable, it is generally known that participants of cohort studies are more often health-conscious compared to individuals who do not participate in a cohort study. Furthermore, most of the cohort studies included in the review were conducted in the United States, and few studies were performed in Europe. Possibly, generalization to the population at risk for colorectal cancer in Europe might not hold as dietary supplement use is much lower when compared to use in the United States, [43,44] and populations in Europe might therefore have other habits and health beliefs than the American population. Nevertheless, systematic reviews provide an exhaustive summary of the current literature, and are considered as the best type of studies for answering a research question if the internal validity is high. [45] Therefore, our findings with regard to the association between dietary supplement use and colorectal cancer risk are assumed to be generalizable to the populations under study.

Individuals with sporadic colorectal adenomas

In the POLIEP follow-up study, the prevalence of colorectal adenoma recurrence and recurrence of adenomas with advanced pathology was 29% and 7% respectively. These proportions are highly comparable with the prevalence of nonadvanced (32%) and advanced (7%) adenoma recurrence based on data from 2,990 consecutive patients newly diagnosed with adenomas from a community based surveillance practice in the Netherlands. [46]

Nevertheless, representativeness of our findings to the whole population with a history of sporadic colorectal adenomas may not hold as recruitment was only possible via outpatient clinics in participating hospitals, and patients with undetected adenomas could be missed in this study due to the asymptomatic condition of colorectal adenomas. [35] Therefore, our findings might only be translated to all patients with a history of sporadic colorectal adenomas who were treated in outpatient clinics in hospitals.

Also, in recurrence studies, a selection of the study population with a previous occurrence of the event is studied, which increases the possibility for index-event bias. [47-50] In this

type of selection bias, common (combinations of) risk factors are responsible for the risk of both occurrence and recurrence of the disease, e.g. colorectal adenomas. [48,49,51] Due to the dependency between risk factors related to the selection of participants based on the occurrence of a first adenoma, the association between dietary supplement use and adenoma recurrence might be attenuated or deattenuated. Furthermore, our findings could be influenced by differences in risk factor profiles as a family history of colorectal cancer was more often reported in this study (25%) when compared to the general population (10–15%). [52] Among those individuals with a family history of colorectal cancer, a larger proportion of women and a higher use of dietary supplements were present, which possibly indicates different combinations of risk factors. According to Dahabreh and Kent, [47] partial control for index-event bias may be achieved by adjusting for important risk factors. In our study, several potential confounders in the association between dietary supplement use and colorectal adenoma recurrence were evaluated, but caution in the interpretation of our results is warranted as many potential risk factors remain unknown.

Individuals with Lynch syndrome

In the GeoLynch cohort study, Lynch syndrome carriers were mainly identified via linkage to a hereditary tumor registration of the NFDHT. The NFDHT registers families with a high risk of developing hereditary cancers, including Lynch syndrome, and aims to promote and coordinate periodic surveillance and screening of those high risk families. However, a selection of the total Lynch syndrome population could be registered more often as carriers could be more aware of their health status and disease risk, and may therefore have a healthier diet, lifestyle, and a higher social economic status compared to those who are not registered. Nevertheless, earlier publications in this cohort showed that those factors are comparable between individuals with Lynch syndrome and the general population. [53,54] Furthermore, individuals with Lynch syndrome in our cohort may not be representative to all families with Lynch syndrome in the Netherlands. It might be that some family members of the identified families could not be traced by the registry leading to incomplete families in the database of the NFDHT. Therefore, our results regarding dietary supplement use and colorectal adenoma risk might not be generalizable to the whole Lynch syndrome population.

Individuals with colorectal cancer

Despite the relatively low number of colorectal cancer patients in the COLON study in this thesis so far, our findings regarding the consistency of dietary supplement use after colorectal cancer diagnosis could probably be translated to most of the individuals with colorectal cancer in the Netherlands as we included a heterogeneous group of patients with different disease stages and different cancer therapies. Based on data from the Dutch Cancer Registry, several characteristics of participants in the COLON study correspond to those of colorectal cancer patients in the general population who did not participate (**Table 7.3**). For disease stage specifically, proportions of stage I, II, or III colorectal cancer patients in the COLON study are comparable with disease stages of colorectal cancer patients in the general population. However, as already mentioned in **chapter 6** of this thesis, stage IV colorectal cancer patients were probably underrepresented since they were not always invited for our study due to medical and ethical concerns. Therefore, our findings might only be representative to patients who suffer from colorectal cancer in stage I, II, or III of the disease.

Table 7.3 Comparison of characteristics of colorectal cancer patients in the COLON study with colorectal cancer patients in the general population according to the Dutch Cancer Registry

Characteristic	Colorectal cancer patients in the general population (n=796)	Colorectal cancer patients in the COLON study[¥] (n=189)
Mean age (y)	69	67
Sex (men (%))	53	60
Disease stage (%)		
I	23	28
II	28	28
III	26	30
IV	18	10
Unknown	5	5
Location of the tumor (%)		
Colon	59	65
Rectum	41	35

[¥] Colorectal cancer patients included in the COLON study until 31 December 2012.

OVERALL CONCLUSION

This thesis describes the results of a systematic literature review with meta-analyses, and three prospective cohort studies in order to investigate the role of dietary supplement use and colorectal tumor etiology and recurrence in the general population and in high-risk populations for colorectal cancer. Our results do not point toward a preventive nor a harmful role of dietary supplement use in colorectal tumor risk and recurrence in the general population and in high-risk populations for colorectal cancer, and are therefore not recommended for primary or tertiary prevention of colorectal cancer. Furthermore, dietary supplement use appears to be inconsistent over time after colorectal cancer diagnosis, and use should be repetitively assessed over time. Thus, in line with the recommendations regarding dietary supplement use in the prevention of cancer from the WCRF/AICR, [4] it is unwise to recommend widespread supplement use as a means of colorectal tumor prevention.

IMPLICATIONS FOR PUBLIC HEALTH AND CLINICAL PRACTICE

Given the fact that dietary supplement use is rising in countries where colorectal tumors are prevalent and the incidence of colorectal tumors will increase due to screening practices, research on the role of dietary supplement use for primary or tertiary prevention of colorectal tumors should continue. Several recommendations for public health and for clinical practice about the role of dietary supplement use in primary or tertiary prevention for colorectal tumors in high-risk populations for colorectal cancer could be made.

Implications for public health

The results in this thesis showed no (**chapters 3 and 4**) or inconsistent associations (**chapter 2**) between dietary supplement use and colorectal tumor risk or recurrence in high risk populations for colorectal cancer. Nowadays, many individuals, including those at high risk for colorectal tumors, show considerable interest in self-acquired information on 'self-medication', e.g. dietary supplement use, via family, friends, books, or the internet for primary or tertiary prevention of a potential disease. However, it could be questioned if the 'hype' on taking dietary supplements is useful for chronic diseases, including primary or tertiary prevention of colorectal cancer. Nevertheless, based on the findings in this thesis and in line with the expert guidelines of the WCRF/AICR, [4] use of dietary supplements is not

recommended for the prevention of colorectal tumors. According to several recent meta-analyses of randomized clinical trials and/or prospective cohort studies on other chronic diseases, inconclusive results were found for dietary supplement use and cardiovascular disease risk, [55,56] stroke, [57-60] hip fracture risk, [61,62] osteoporosis, [63,64] or glycemic control in diabetes. [65] Furthermore, commercially available supplements are considered as non-toxic, but there are a number of commonly used supplements available that contain high doses of certain vitamins and minerals that exceed the tolerable upper intake levels as established by the European Food and Safety Authority (EFSA). [66] A daily consumption of these products during longer periods cannot exclude a possible occurrence of detrimental effects on health and wellbeing, such as neurological symptoms and increased risk of blood clotting. [67] Nevertheless, supplementation could be useful for specific target groups who have or are at high risk for micronutrient deficiencies or who need extranutritional support by means of dietary supplements, such as folic acid for women who are or want to become pregnant, vitamin D for lactating women, babies, young children, and (frail) elderly, and supplemental iron and vitamin B12 for vegetarians and vegans. Thus, it is highly warranted to acquire more insight in the sense and nonsense of dietary supplement use in relation to primary and tertiary prevention of chronic diseases, including colorectal tumors, by conducting large and long-term prospective cohort studies in which dietary supplement use will be extensively and repetitively assessed over time.

Implications for clinical practice

Neither a preventive nor a harmful role for dietary supplement use and colorectal tumor risk or recurrence in high-risk populations for colorectal cancer was indicated in this thesis. Dietary supplement use is common among patients who are at high risk or who are suffering from chronic illnesses, such as colorectal tumors. [68-74] For many patients, taking dietary supplements may be a way to regain some control over their health and treatment of their illness. [75] Unfortunately, clinicians are not often aware of their patients' use of supplements, and their underlying motivations or anxieties for potential benefits or risks of use. Also, the studies in this thesis did not evaluate the role of dietary supplements during active treatment for colorectal cancer. It is suggested that some types of supplements could interact with conventional cancer treatments, [76-82] which might be harmful for patients with established colorectal cancer. It is of great importance to acquire consistent evidence about the long-term benefits and risks of dietary supplement use prior to advices by clinicians, for example by conducting large and long-term prospective cohort studies

or randomized controlled trials which assess the efficacy of a specific dietary supplement on the occurrence or recurrence of cancers, such as colorectal cancer. Hence, clinicians should yet discourage dietary supplement use in patients at high risk for colorectal tumors.

FUTURE RESEARCH PERSPECTIVES

Based on the current evidence and the conclusions in this thesis, several possibilities for future research should be addressed before uniform public health policies on dietary supplement use and colorectal tumor risk and recurrence can be composed. The main message is that future studies should first aim to get more insight into the role of dietary supplement use in relation to colorectal tumor risk and recurrence by extensively assessing dietary supplement use repetitively over time whereby the long-term benefits and risks of dietary supplement use become clear.

Several future research opportunities are given below.

- The increasing use of self-prescribed dietary supplements as 'self-medication' for primary and tertiary prevention of colorectal tumors urges the need to adequately assess the habitual use of dietary supplements by means of a comprehensive and detailed questionnaire by taking type of supplement, frequency of intake, amount of intake, unit of intake, duration of use, dosage, brand name and ingredients of the supplement into account. Other future research opportunities should capitalize on new electronic technologies to assess dietary supplement use, e.g. newly developed methods for recall of dietary supplement use, or apps for nutritional research for tablet or smartphone.
- It should be investigated if and how a dietary supplement questionnaire can be validated. The use of biomarkers, such as serum beta-carotene, serum alpha-tocopherol, plasma vitamin c and urinary calcium, are inappropriate for the validation of a dietary supplement questionnaire as those biomarkers are a combination of nutrient intakes from foods and supplements and supplements are often mixtures of nutrients, e.g. multivitamins or antioxidant mixtures. Therefore, another and also less comprehensive option for the validation of a dietary supplement questionnaire could be the use of a 'golden standard' by for example photographing or making photocopies of the supplement bottle labels during in-person interviews.

- More insight into the consistency of dietary supplement use is needed before associations between dietary supplement use and colorectal tumor risk in high-risk populations, and recurrence or survival in colorectal cancer patients, or any other health outcome in the general population, can be prospectively examined. Future prospective cohort studies should focus on repetitive assessments of dietary supplement use, since use appeared to be inconsistent over time after colorectal cancer diagnosis in this thesis. For data-analyses of repeated measures of dietary supplement use over time, repeated-measures ANOVA is widely used for the analysis of repeated-measures data, such as dietary supplement use. Furthermore, mixed-effects models use all available data, and can properly account for correlation between repeated measurements on the same subject [83].
- In order to gain more insight into the role of dietary supplement use among colorectal cancer survivors in Europe, but also among individuals with Lynch syndrome and individuals with a history of colorectal adenomas, large and long-term prospective cohort studies need to be combined in order to increase the power. In this way, associations between dietary supplement use over time and treatment, recurrence of the disease and survival could be investigated when repetitive and extensive assessment of dietary supplement use will be applied. The COLON study, which is the first European prospective cohort study among colorectal cancer survivors, will be combined with other studies among colorectal cancer survivors in Europe in order to investigate whether associations between dietary supplement use and progression of the disease among colorectal cancer patients differ between several cancer therapies and disease stages. Furthermore, the GeoLynch cohort study will be expanded and current and future participants will be longer prospectively followed.
- The lack of association between dietary supplement use and colorectal adenoma risk in individuals with Lynch syndrome needs to be confirmed by other prospective cohort studies among Lynch syndrome patients as the study described in this thesis was the first prospective cohort study that evaluated this association.

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Chapter 8

Summary

SUMMARY

Dietary supplement use has exploded over the past decades. Nowadays, a wide range of dietary supplements is commercially available. Many individuals show considerable interest in self-acquired information on dietary supplement use via family, friends, books, or the internet. Consumers have access to an enormous selection and a diverse variety of dietary supplements in several combinations and in different dosages. Many individuals believe that taking dietary supplements may be beneficial in the treatment of acute or chronic illnesses, or for the prevention or recurrence of a serious disease, and use may be perceived as a way to regain some control over their own health, illness, or treatment. However, it is still unclear if long-term use of dietary supplements is beneficial or harmful on overall health and chronic disease, including cancer.

The World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) advises against the use of supplements for cancer prevention, and recommends to meet nutritional needs through diet alone. However, this recommendation is mainly based on randomized controlled trials among those at a relatively high risk of lung cancer, and men with a high risk of prostate cancer. Also, those trials provided specific dietary supplements in fixed and high dosages, which makes it difficult to generalize the findings to other populations. Up to now, it is not yet clear whether this recommendation for habitual dietary supplement use also applies to the general population.

The role of dietary supplement use in relation to colorectal cancer risk in the general population has been studied comprehensively in observational prospective and retrospective studies. However, firm conclusions are still missing. Important gaps of knowledge exist with regard to dietary supplement use and colorectal tumor incidence and recurrence in high-risk populations for colorectal tumors, i.e. those with a history of sporadic colorectal adenomas, those with Lynch syndrome, and patients diagnosed with colorectal cancer. As a consequence, it is yet unclear if the recommendation regarding use of dietary supplements from the WCRF/AICR also applies to high-risk populations for colorectal tumors. Among individuals with established colorectal cancer, it is plausible that dietary supplement use may vary after diagnosis and during or after cancer therapy as many colorectal cancer patients take dietary supplements after diagnosis, during or after cancer therapy in order to prevent recurrence of the disease and to improve their well-being and prognosis. Therefore, it is of great importance to get more insight into the role of dietary supplement use on risk of colorectal tumors in the general population and

in high-risk populations for colorectal tumors, because dietary and lifestyle factors – and thereby also dietary supplement use – are the most associated with colorectal tumors compared to other types of cancer.

The overall aim of this thesis is to improve our knowledge about the role of dietary supplement use in colorectal tumor development in the general population and in populations at high risk for colorectal tumors, and to gain insight into the consistency of dietary supplement use over time in patients diagnosed with colorectal cancer.

Chapter 2 describes a systematic literature review and meta-analyses of prospective cohort studies in the general population on the association between dietary supplement use and colorectal cancer risk. In this systematic literature review, prospective cohort studies until January 2013 were included. Meta-analyses showed that inverse associations between multivitamin use, calcium supplement use and colorectal cancer risk were found, but inconsistent associations were shown for use of supplemental vitamin A, vitamin C, vitamin D, vitamin E, folic acid and garlic and risk of colorectal cancer.

The role of dietary supplement use in relation to colorectal tumor risk in high-risk populations has been investigated in two prospective cohort studies, i.e. the POLIEP follow-up study (**chapter 3**) and the GeoLynch cohort study (**chapter 4**). In the POLIEP follow-up study, 565 individuals with at least one histologically confirmed colorectal adenoma were followed, and information on diet, lifestyle and medical characteristics was collected. In that study, the association between dietary supplement use, total colorectal adenoma recurrence and advanced adenoma recurrence was examined during a median person time of 5.4 years. One third of the total study population used a dietary supplement. Furthermore, about one third of the total study population had at least one colorectal adenoma recurrence, and of these, 37 patients had at least one advanced adenoma. Compared to no use, dietary supplement use was not statistically significantly associated with total colorectal adenoma recurrence, nor with recurrent advanced adenomas. However, the findings should be interpreted with caution due to the low number of users of specific dietary supplements and the number of cases with advanced adenomas.

Using data of 470 individuals with Lynch syndrome in the GeoLynch cohort study, associations between dietary supplement use and colorectal adenoma risk were evaluated during a median person time of 39.1 months. Of the total study population, 40% used a dietary supplement, and 26.0% developed a colorectal adenoma. Use of any dietary supplement was not statistically significantly associated with colorectal adenoma risk. Due

to the relatively small numbers of individuals with Lynch syndrome in this study, further research is warranted to determine whether or not dietary supplement use is associated to colorectal adenoma and colorectal cancer risk in MMR gene mutation carriers. Future studies among individuals with a history of colorectal adenomas and among individuals with Lynch syndrome is needed in which dietary supplement use will be extensively assessed.

In order to explore whether or not dietary supplement use varies over time among individuals with established colorectal cancer, a new prospective cohort study, i.e. the COLON study, has been set up. The design of the COLON study is described in **chapter 5**. In **chapter 6**, the consistency of dietary supplement use at diagnosis, six months and two years post-diagnosis was assessed among 160 colorectal cancer patients. This study demonstrated that dietary supplement use among colorectal cancer patients is common, but use varied over time after diagnosis, during and after cancer therapy. About one third of the colorectal cancer patients used dietary supplements at diagnosis and two years post-diagnosis, while about half of the patients used supplements six months diagnosis, i.e. during cancer therapy. Furthermore, patients took different types of supplements over time, which also indicates that dietary supplement use is inconsistent. Dietary and lifestyle factors, sociodemographic and disease related characteristics of consistent users were similar to inconsistent users and consistent nonusers. On the basis of those findings, observational studies among colorectal cancer patients should repetitively assess use after cancer diagnosis in order to obtain a good estimate of dietary supplement use after diagnosis, during and after cancer therapy.

The results in this thesis do not point toward a preventive nor a harmful role for dietary supplement use in colorectal tumor risk and recurrence in the general population and in high-risk populations for colorectal cancer. Therefore, dietary supplement use is not recommended for primary or tertiary prevention of colorectal cancer. Furthermore, dietary supplement use appeared to be inconsistent over time after colorectal cancer diagnosis, during and after cancer therapy. Since dietary supplement use is rising in countries where colorectal tumors are prevalent and the incidence of colorectal tumors will increase due to screening practices, research on the role of dietary supplement use for primary or tertiary prevention of colorectal tumors should continue in which use should be repetitively and comprehensively assessed in future large and long-term prospective cohort studies. Also, it is needed that underlying mechanisms and potential interactions between conventional cancer treatments and dietary supplement use in relation to colorectal tumor risk become

clear in future research. In this way, recommendations for public health and clinical practice on the association between dietary supplements and primary or tertiary prevention of colorectal tumors in the general population and in high-risk populations for colorectal cancer could be made.

Chapter 9

Samenvatting
(Summary in Dutch)

SAMENVATTING

Het gebruik van voedingssupplementen is enorm toegenomen de afgelopen decennia. Tegenwoordig is een breed assortiment voedingssupplementen verkrijgbaar bij de apotheek, de drogist, de supermarkt en op het internet. Consumenten kunnen kiezen uit allerlei soorten voedingssupplementen in diverse combinaties en verschillende doseringen. Vaak worden voedingssupplementen gebruikt in de veronderstelling dat dit gunstig is voor de gezondheid en om ernstige ziektes, zoals kanker, te voorkomen of te behandelen. Het is echter nog onduidelijk of langdurig supplementgebruik gunstig of ongunstig is voor de gezondheid.

Het Wereld Kanker Onderzoeks Fonds en het Amerikaans Instituut voor Kanker Onderzoek (WCRF/AICR) bevelen het gebruik van voedingssupplementen ter preventie van kanker of ter bevordering van de prognose bij kanker niet aan, maar adviseren om de benodigde voedingsstoffen binnen te krijgen via gezonde voeding. Deze aanbeveling is gebaseerd op gerandomiseerde gecontroleerde interventiestudies uitgevoerd bij mensen met een verhoogd risico op long- of prostaatkanker. Tevens werden in deze interventiestudies specifieke supplementen verstrekt met een hoge dosering waardoor de gevonden resultaten lastig te generaliseren zijn. Tot nu toe is het nog onduidelijk of de aanbeveling ook geldt voor 'gewoon' supplementgebruik in de algemene populatie en het risico op colorectale tumoren, zoals colorectale adenomen of carcinomen.

Voedingssupplementgebruik in relatie tot het ontstaan van colorectale tumoren in de algemene populatie is uitgebreid bestudeerd in observationele studies. Echter, eenduidige conclusies ontbreken nog. Tevens is de associatie tussen voedingssupplementgebruik en het risico op het ontstaan van colorectale tumoren bij mensen met een hoog risico, zoals mensen die al eerder een histologisch bevestigd colorectaal adenoom hebben gehad, mensen met het erfelijke Lynch syndroom of mensen die nieuw gediagnosticeerd zijn met colorectaalkanker nog onbekend en daardoor is het reeds onduidelijk of de aanbeveling ten aanzien van voedingssupplementen van het WCRF/AICR kan worden toegepast op deze hoog-risico groepen. Bij mensen met colorectaalkanker is het ook de vraag of voedingssupplementgebruik na de diagnose verandert of juist hetzelfde blijft tijdens of na de behandeling van kanker, aangezien veel colorectaalkankerpatiënten aangeven dat ze voedingssupplementen gaan gebruiken in de hoop dat dit hun gezondheid en prognose verbetert. Het is daarom van groot belang om meer inzicht te krijgen in de invloed van voedingssupplementgebruik op het ontstaan van tumoren in de dikke darm in

de algemene populatie en in de reeds genoemde hoog-risico groepen, omdat voeding en leefstijl – en daardoor wellicht ook voedingssupplementgebruik – het meest geassocieerd zijn met colorectale tumoren in vergelijking met andere soorten kanker.

Het doel van dit proefschrift is te bestuderen of voedingssupplementgebruik een risico op het krijgen van colorectale tumoren beïnvloedt in de algemene populatie en bij mensen met een hoog risico op colorectale tumoren. Tevens willen we inzicht krijgen in de variabiliteit van voedingssupplementgebruik bij mensen die nieuw gediagnosticeerd zijn met colorectaalkanker tijdens en na de behandeling voor kanker.

Allereerst presenteert **hoofdstuk 2** een systematische literatuurstudie met meta-analyses, waarbij de rol van voedingssupplementen op het ontstaan van colorectaalkanker wordt beschreven. In deze literatuurstudie zijn prospectieve cohortstudies tot januari 2013 meegenomen. Uit de meta-analyses kwam naar voren dat multivitaminesupplementen en calciumsupplementen samenhingen met een lager risico op het ontstaan van colorectaalkanker. Voor andere voedingssupplementen met vitamine A, vitamine C, vitamine D, vitamine E, of foliumzuur en knoflookpreparaten werden geen consistente associaties gevonden met het risico op colorectaalkanker.

De rol van voedingssupplementen in relatie tot het ontwikkelen van colorectale tumoren in hoog-risico groepen is onderzocht in twee prospectieve cohortstudies, namelijk de POLIEP-vervolgstudie (**hoofdstuk 3**) en de GeoLynch cohortstudie (**hoofdstuk 4**). Binnen de POLIEP-vervolgstudie zijn bij 565 mensen met tenminste één histologisch bevestigd colorectaal adenoom informatie over voeding en leefstijl en medische gegevens verzameld en is gekeken of het gebruik van voedingssupplementen geassocieerd was met de terugkeer van colorectale adenomen na een mediane persoonstijd van 5,4 jaar. Ongeveer een derde van de totale studiepopulatie gebruikte een voedingssupplement. Tevens had ongeveer een derde van de totale studiepopulatie tenminste één colorectaal adenoom teruggekregen waarvan ruim een vijfde een 'advanced' adenoom bleek te hebben. Voedingssupplementgebruik in het algemeen bleek noch geassocieerd te zijn met de terugkeer van colorectale adenomen in zijn geheel, noch met de terugkeer van 'advanced' adenomen. Echter, voorzichtigheid is geboden bij het trekken van deze conclusies aangezien het aantal gebruikers van voedingssupplementen en het aantal mensen van met name de 'advanced' adenomen laag was.

Binnen de GeoLynch cohortstudie is bij 470 mensen met het Lynch syndroom de associatie bekeken tussen voedingssupplementgebruik en het ontstaan van colorectale adenomen

gedurende een mediane persoonstijd van 39,1 maanden. Van de totale studiepopulatie gebruikte ongeveer 40% een voedingssupplement en 26% ontwikkelde een colorectaal adenoom. Het bleek dat voedingssupplementgebruik niet significant geassocieerd was met het risico op colorectale adenomen. Aangezien de populatie met het Lynch syndroom in dit onderzoek relatief klein was, moet toekomstig onderzoek de resultaten in dit proefschrift bevestigen voordat hieraan conclusies kunnen worden verbonden. Vervolgonderzoek omtrent de ontwikkeling van colorectale tumoren bij mensen met een geschiedenis van colorectale adenomen en bij mensen met het Lynch syndroom is nodig, waarbij voedingssupplementgebruik uitgebreid en gedetailleerd wordt nagevraagd.

Om de stabiliteit van het gebruik van voedingssupplementen te onderzoeken bij mensen bij wie colorectaalkanker is gediagnosticeerd, is er een nieuw prospectief cohortonderzoek opgezet: de COLON studie. De onderzoeksopzet van de COLON studie is beschreven in **hoofdstuk 5**. Vervolgens is in **hoofdstuk 6** onderzocht of het gebruik van voedingssupplementen bij 160 colorectaalkankerpatiënten stabiel is na de diagnose, tijdens en na de kankertherapie. Uit dit onderzoek kwam naar voren dat het gebruik van voedingssupplementen bij colorectaalkankerpatiënten vaak voorkomt, maar het gebruik wisselt vaak tijdens en na de kankertherapie: ruim een derde van de colorectaalkankerpatiënten gebruikte voedingssupplementen op het moment van de diagnose en twee jaar na de diagnose, terwijl ongeveer de helft van de patiënten aangaf supplementen te gebruiken zes maanden na de diagnose, oftewel tijdens de kankertherapie. Verder werden vaak verschillende soorten supplementen na de diagnose, tijdens en na kankertherapie gerapporteerd, wat ook aangeeft dat voedingssupplementgebruik inconsistent is. De consistente niet-gebruikers, inconsistente gebruikers en consistente gebruikers verschilden verder nauwelijks van elkaar wat betreft voeding, leefstijl, sociodemografische en ziektegerelateerde factoren. Naar aanleiding van deze resultaten wordt aanbevolen om het gebruik van voedingssupplementen meerdere keren gedurende de tijd na te vragen in observationele studies om een goede schatting te kunnen maken van het gebruik na de diagnose, tijdens en na de kankertherapie.

De bevindingen uit dit proefschrift wijzen niet op een gunstige of ongunstige rol van voedingssupplementgebruik in relatie tot het ontwikkelen van colorectale tumoren in de algemene populatie en in hoog-risico groepen voor colorectaalkanker. Daarom worden voedingssupplementen niet aanbevolen voor de primaire of tertiaire preventie van colorectaalkanker. Verder bleek dat het gebruik van voedingssupplementen bij colorectaalkankerpatiënten varieert na de diagnose, tijdens en na kankertherapie. Vanwege het feit dat

voedingssupplementgebruik nog steeds stijgt in landen waar colorectale tumoren veel voorkomen – ook mede dankzij de recent ingevoerde screening op colorectale tumoren – moet toekomstig observationeel onderzoek naar de rol van voedingssupplementgebruik in relatie tot primaire of tertiaire preventie worden voortgezet. In toekomstige prospectieve cohortonderzoeken moet de nadruk komen te liggen op het herhaaldelijk navragen van voedingssupplementgebruik door middel van een uitgebreide en gedetailleerde vragenlijst gericht op voedingssupplementen. Daarnaast is het nodig dat onderliggende mechanismen en eventuele interacties tussen conventionele kankertherapieën en voedingssupplementen in relatie tot het ontstaan van colorectale tumoren duidelijk wordt in toekomstig onderzoek. Op deze manier kunnen aanbevelingen voor de volksgezondheid en de klinische praktijk ten aanzien van de rol van voedingssupplementen voor primaire of tertiaire preventie van colorectale tumoren in de algemene populatie en bij mensen met een hoog risico op colorectaalkanker worden opgesteld.

Dankwoord

DANKWOORD

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About the author

CURRICULUM VITAE

Renate Carmen Heine-Bröring was born on August 4, 1982 in Willemstad, Curaçao (Netherlands Antilles). In 2001, she completed secondary school (Athenaeum) at Esdal College in Emmen (NL), and started studying Health Sciences at Maastricht University (NL). After completing her propaedeutic in 2002, Renate entered the program of Nutrition and Dietetics at the Hanze University of Applied Sciences in Groningen (NL). For this study, she did paramedical internships at 's Lands Hospital & Sint Vincentius Hospital in Paramaribo (Surinam), VU University Medical Center in Amsterdam (NL), and University Medical Center Groningen in Groningen (NL). After graduating in 2006, Renate did the premaster Health Sciences at VU University in Amsterdam (NL) after which she started a MSc program in Nutrition and Health at the Division of Human Nutrition of Wageningen University (NL) in 2007, specializing in the field of Nutritional and Public Health Epidemiology. During her master program, Renate was a scientific intern at the Fred Hutchinson Cancer Research Center in Seattle (USA). Furthermore, her master thesis focused on intake of fish and marine n-3 fatty acids in relation to coronary calcification in cooperation with Erasmus University Medical Center in Rotterdam and Wageningen University (NL). After graduating in 2009, Renate was appointed as a PhD-candidate in the Diet and Cancer group of Professor Ellen Kampman at the Division of Human Nutrition of Wageningen University (NL) which was funded by World Cancer Research Fund (WRCF-International & WCRF-NL). The overall aim of this PhD-project was to improve the knowledge about the role of dietary supplement use in colorectal tumor development in the general population and in populations at high risk for colorectal tumors, and to gain insight into the consistency of dietary supplement use over time in patients diagnosed with colorectal cancer. As a PhD-candidate, Renate joined the educational program of the Graduate School VLAG, and she was a member of the PhD-committee at the division. Also, she was involved in teaching and supervising students at the BSc and MSc level. Furthermore, she participated in the PhD-tour to the Nordic Countries, i.e. Denmark, Sweden, and Finland in 2009. In 2011, she received a WCRF fellowship which enabled her to follow the International Course in Nutritional Epidemiology at Imperial College in London (UK). Currently, Renate is working as a lecturer in Nutrition and Dietetics at the Hanze University of Applied Sciences in Groningen (NL).

LIST OF PUBLICATIONS

Publications in peer-reviewed journals

Heine-Bröring RC, Winkels RM, Renkema JMS, Kragt L, van Orten-Luiten ABC, Tigchelaar EF, Chan DSM, Norat T, Kampman E. Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies. Int J Cancer. 2015 May 15;136(10):2388-401

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Jung A, van Duijnhoven FJ, Nagengast FA, Blom H, Botma A, **Heine-Bröring RC**, Kleibeuker J, Vasen H, Harryvan J, Winkels RM, Kampman E. Dietary B vitamin and methionine intake and MTHFR C677T genotype on risk of colorectal tumors in patients with Lynch syndrome: The GEOLynch Cohort Study. Cancer Causes Control. 2014 Sep;25(9):1119-29

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Knopperts AP, Nielsen M, Niessen RC, Tops CM, Jorritsma B, Varkevisser J, Wijnen J, Siezen CL, **Heine-Bröring RC**, van Kranen HJ, Vos YJ, Westers H, Kampman E, Sijmons RH, Hes FJ. Contribution of bi-allelic germline MUTYH mutations to early-onset and familial colorectal cancer and to low number of adenomatous polyps: case-series and literature review. Fam Cancer. 2013 Mar;12(1):43-50

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Heine-Bröring RC, Brouwer IA, Proença RV, van Rooij FJ, Hofman A, Oudkerk M, Witteman JC, Geleijnse JM. Intake of fish and marine n-3 fatty acids in relation to coronary calcification: the Rotterdam Study. Am J Clin Nutr 2010;91 (5):1317-23

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Submitted publications

Heine-Bröring RC, Winkels RM, Van Duijnhoven FJB, Kok DEG, Van Zutphen M, Van Halteren HK, Kouwenhoven EA, Kruyt PhM, Spillenaar Bilgen EJ, De Wilt JHW, Kampman E. Consistency of dietary supplement use among colorectal cancer patients from diagnosis until two years post-diagnosis.

OVERVIEW OF COMPLETED TRAINING ACTIVITIES

Discipline specific activities	
Courses	
Advanced course 'Exposure Assessment in Nutrition Research', Wageningen University, Wageningen, the Netherlands	2010
Masterclass 'Linear and logistic regression, Wageningen University, Wageningen, the Netherlands	2010
Training Systematic Literature Review and Meta-analyses, Imperial College London, London, UK	2010
Training Nijmegen RUCO, Radboud University Nijmegen, Nijmegen, the Netherlands	2010–2011
International Course in Nutritional Epidemiology, Imperial College, London, UK	2011
Masterclass 'Multilevel analysis', Wageningen University, Wageningen, the Netherlands	2011
Masterclass Analysis in R, Wageningen University, Wageningen, the Netherlands	2012
Survival Analyses, NIHES, Erasmus University, Rotterdam, the Netherlands	2012
Basic Oncology, Introduction in fundamental & clinical oncology, Dutch Association for Oncology, Ellecom, the Netherlands	2012
Masterclass Longitudinal data analysis, Wageningen University, Wageningen, the Netherlands	2013
Conferences & symposia	
CIMPosium Maastricht, Maastricht University, Maastricht, the Netherlands	2010
WEON, Nijmegen, the Netherlands	2010
WEON, IJmuiden, the Netherlands Oral presentation COLON study, EYE session Poster presentation POLIEP follow-up study	2011
Colorectal cancer symposium, Rotterdam, the Netherlands	2011
Food for Thought, Gelderse Vallei Ede, Ede, the Netherlands	2011–2014
General courses	
VLAG PhD week, Wageningen University, Wageningen, the Netherlands	2009
Teaching and supervising thesis students, Educational Staff Development, Wageningen University, Wageningen, the Netherlands	2010
Mini symposium: How to write a World class paper, Library, Wageningen University, Wageningen, the Netherlands	2010
Research retreat, Wageningen University, Wageningen, the Netherlands	2010
Competence assessment, Wageningen University, Wageningen, the Netherlands	2011
Scientific Writing, Wageningen University, Wageningen, the Netherlands	2013
Philosophy and Ethics of Food Science and Technology, Wageningen University, Wageningen, the Netherlands	2013
Career Orientation, Wageningen University, Wageningen, the Netherlands	2013
Optional activities	
Concepts and Methods in Epidemiology, Wageningen University, Wageningen, the Netherlands	2008–2010
PhD tour to the Nordic Countries (Denmark, Sweden, Finland), Wageningen University, Wageningen, the Netherlands Oral presentation at University of Kuopio	2009
Workshop mind-mapping, Wageningen University, Wageningen, the Netherlands	2010
Epi-research, Wageningen University, Wageningen, the Netherlands	2009–2014
Preparation of Research Proposal, Wageningen University, Wageningen, the Netherlands	2009–2014
Journal Club "A bite into cancer", Wageningen University, Wageningen, the Netherlands	2010–2014
Staff seminars, Wageningen University, Wageningen, the Netherlands	2010–2014

Colophon

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