RESEARCH

Levothyroxine use and the risk of colorectal cancer: a large population-based case–control study

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Abstract

Objective: Whether an association between oral levothyroxine use, leading to supraphysiological exposure of the colon to thyroid hormones, and risk of colorectal cancer exists in humans is unclear. We therefore aimed to assess whether the use of levothyroxine is associated with a reduced risk of colorectal cancer in a linked cohort of pharmacy and cancer data.

Design: Population-based matched case–control study.

Methods: A total of 28,121 patients diagnosed with colorectal cancer between 1998 and 2014 were matched to 106,086 controls. Multivariable logistic regression was used to estimate the association between levothyroxine use and occurrence of colorectal cancer, adjusted for potential confounders. Results were stratified by gender, age, tumour subtype, and staging, as well as treatment duration and dosing.

Results: A total of 1066 colorectal cancer patients (4%) and 4024 (4%) controls had used levothyroxine at any point before index date (adjusted odds ratio 0.95 (0.88–1.01)). Long-term use of levothyroxine was seen in 323 (30%) colorectal cancer patients and 1111 (28%) controls (adjusted odds ratio 1.00 (0.88–1.13)). Stratification by tumour subsite showed a borderline significant risk reduction of rectal cancer, while this was not seen for proximal colon cancer or distal colon cancer. There was no relationship with treatment duration or with levothyroxine dose.

Conclusions: In this study, no reduced risk of colorectal cancer was seen in levothyroxine users. When stratifying by tumour subsite, a borderline significant risk reduction of rectal cancer was found and may warrant further research.

Introduction

Primary hypothyroidism is a common condition with a rapidly rising global prevalence. In the Netherlands, the prevalence of overt hypothyroidism has increased from 0.4 to 2.9% over the past 15 years (1) (www.nivel. nl/nl/nivel-zorgregistraties-eerste-lijn/jaarcijfers-aandoeningen-incidenties-en-prevalenties). Treatment of primary hypothyroidism consists of hormone substitution therapy with daily oral administration of the synthetic thyroid hormone levothyroxine. The majority of levothyroxine is absorbed in the upper gastrointestinal tract, ranging from 40 to 80% (2). Consequently, 20 to 60% of this synthetic drug is excreted in the stool, resulting in a supraphysiological exposure of the colonic epithelium to thyroid hormone.

Thyroid hormones (TH) play an important role in cellular growth, proliferation, and differentiation (3). Alterations in TH bioavailability have been implicated in the development of several forms of cancer, including basal cell carcinomas (4), lung cancer (5, 6), and colorectal cancer (CRC) (7). CRC is one of the world's most common cancers, with an estimated global number of 1.8 million diagnoses each year (8). Interestingly, it has been shown that in CRC, intracellular TH concentrations are reduced due to upregulation of the TH-inactivating enzyme deiodinase type III (Dio3) (7), whereas increased intracellular levels of TH led to a potent reduction in the growth rate of human colorectal tumour cell lines (9). This raises the question whether levothyroxine users are protected against CRC development due to supraphysiological intestinal concentrations of TH.

Previous studies have explored the association between the use of levothyroxine and the risk of CRC but have shown conflicting results. Some studies found evidence for a protective effect of levothyroxine, while others found no association (10, 11, 12, 13). Furthermore, some of these studies are limited by including a relatively small number of patients, relying on self-reported information, and lacking details on the dose and duration of levothyroxine use as well as tumour location and staging.

Therefore, in this study, we investigated whether the use of levothyroxine is associated with a reduced risk of CRC and whether such effect is associated with dose and duration of levothyroxine use. In addition, differences in tumour location were assessed as well since clinical features of CRC may vary depending on the anatomical site.

Materials and methods

Data sources

Data from the Netherlands Cancer Registry (NCR) were linked on a patient-level to the Out-patient Pharmacy Database of the PHARMO Database Network.

The NCR is a population-based registry that is maintained by the Comprehensive Cancer Centre the Netherlands and comprises information on newly diagnosed cancer patients in the Netherlands. The NCR is notified of new patients with cancer by pathology departments, general hospitals, and radiotherapy institutes. On a daily basis, trained data managers register data from hospital records within all Dutch hospitals using the NCR's registration and coding manual.

The Out-patient Pharmacy Database of the PHARMO Database Network comprises general practitioner (GP) or specialist prescribed healthcare products dispensed by the outpatient pharmacy. The dispensation records include information on the type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensations are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/atc_ddd_index/).

The cohort resulting from this linkage covers a catchment area of the PHARMO Database Network representing approximately 4.2 million residents (~25% of the Dutch population) that all have complete information available on GP or specialist prescribed healthcare products dispensed by the outpatient pharmacy. Detailed information on the methodology of the used record linkage method can be found elsewhere (14, 15, 16).

Study population

All subjects who were diagnosed in the period between 1998 and 2014 with primary CRC (ICD 10-CM code C18-C20) were identified. The first date of CRC diagnosis was defined as the index date. To reduce the likelihood of including patients with heritable CRC syndromes, patients younger than 40 years of age at diagnosis were excluded.

Each CRC case was randomly matched to between one and four controls based on sex, birth year (with a variation of 2 years), zip code, and start year of enrolment in the Out-patient Pharmacy Database (to ensure equal time windows to measure exposure). Matched controls received the same index date as their matched CRC case. Cases and controls were not allowed to have a diagnosis of cancer before the index date. Furthermore, controls had to be alive and

known in the Out-patient Pharmacy Database at index date and could not be matched more than once.

Exposure definition

Of all CRC cases and their matched non-cancer controls, all levothyroxine dispensations (ATC code H03AA01) prior to the index date were extracted from the Out-patient Pharmacy Database. Use of levothyroxine was defined as having at least one dispensation of levothyroxine at any time point prior to the index date. Treatment episodes of uninterrupted levothyroxine were constructed based on quantity dispensed and prescribing information to assess the cumulative days of exposure. In case of an interruption between two dispensations, use of levothyroxine was considered uninterrupted if the duration of this gap was less than half the period of the given dispensation, according to the method of Catalan and LeLorier (17). Timing of initiation was defined as the first dispensation of levothyroxine prior to the index date.

Furthermore, the total cumulative dose of levothyroxine was calculated as the sum of all dispensed doses during the levothyroxine episodes prior to the index date and expressed in milligram.

Statistical methods

Characteristics of CRC cases and their matched non-cancer controls were reported descriptively. Differences in characteristics were assessed using chi-square tests for categorical variables and ANOVA tests for continuous variables.

Multivariable logistic regression was used to estimate the odds ratio (OR) and two-sided 95% CI for CRC with the use of levothyroxine, adjusted for drugs that potentially decrease the risk of CRC including use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, antidiabetics (both oral antidiabetics and insulin), hormone replacement therapy, and oral contraceptives. Non-users of levothyroxine served as the reference group for all analyses. Analyses were conducted stratified by timing of initiation, cumulative dose, and cumulative duration of use. Furthermore, the association between CRC and use of levothyroxine was examined stratified by age, gender, tumour stage, and tumour subsite. To enable stratification by tumour stage and subsite, all non-cancer controls were provided with artificial tumour information similar to their matched CRC case. Proximal colon cancers included malignant neoplasms of the cecum, appendix, ascending colon,

hepatic flexure, and transverse colon. Distal colon cancers included malignant neoplasms of the splenic flexure, descending colon, and sigmoid colon. Rectal cancer included malignant neoplasm of the rectum.

All data were analysed using SAS programs organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.4.

Results

A total of 28,121 patients with CRC could be matched to 106,086 non-cancer controls. Baseline characteristics of study participants are provided in Table 1. As a result of matching on birth year with a variation of 2 years, patients with CRC were statistically significantly younger compared to non-cancer controls (69.6 years vs 71.1 years, $P < 0.0001$); however, this is not a clinically relevant difference. The mean available observation period prior to the index date was 7.3 years for CRC cases and 7.4 years for non-cancer controls ($P < 0.01$).

At the time of initial diagnosis, the majority of all tumours had grown into the outermost layers of the colon or rectum but had not spread to distant sites (stage II and stage III disease both account for 29% of all tumours). A primary tumour located in the proximal colon was seen in 33% of the CRC patients, 32% had a primary tumour in the distal colon, 29% in the rectum, and 4% in the rectosigmoid junction. Furthermore, the use of medication prior to index date that is potentially associated with a reduced risk of CRC was lower among non-cancer controls compared to CRC cases ($P < 0.001$). Table 2 provides the overall OR for levothyroxine use and the risk of CRC. All results were adjusted for the use of comedications (including aspirin, NSAIDs, statins, antidiabetics, hormone replacement therapy, and oral contraceptives) that are potentially associated with a reduced risk of CRC. A total of 1066 CRC cases (4%) had used levothyroxine at any point before the index date compared to 4024 (4%) non-cancer controls. A modestly increased risk of CRC was seen among those initiating levothyroxine in the 2 years before the index date, albeit not significant (OR 1.12 (95% CI 0.97–1.290). Among levothyroxine users, 342 CRC cases (32%) and 1338 non-cancer controls (33%) had used levothyroxine for less than 2 years (adjusted OR 0.94 (95% CI 0.83–1.06)). Use of levothyroxine for more than 6 years was seen among 323 (30%) CRC cases compared to 1111 (28%) non-cancer controls, yielding an adjusted OR of 1.00 (95% CI 0.88–1.13) for CRC associated with long-term use of levothyroxine.

Table 1 Characteristics of colorectal cancer cases and matched non-cancer controls.

	Colorectal cancer cases, $N = 28,121$	Non-cancer controls, $N = 106,086$	*P*-value
Age (years), *n* (%)			
<75	17,638 (63)	60,942 (57)	<0.0001
≥75	10,483 (37)	45,144 (43)	<0.0001
mean (±s.d.)	69.6 ± 11.5	71.1 ± 11.5	<0.0001
Gender, male, *n* (%)	15,892 (57)	59,625 (56)	0.35
Available observation time period before index date			
mean (±s.d.)	7.3 ± 4.1	7.4 ± 4.1	<0.01
Tumour stage, *n* (%)			
I	4962 (18)	NA	*NA*
II	8041 (29)	NA	NA
III	8009 (29)	NA	NA
IV	5958 (21)	NA	NA
Unknown	1151 (4)	NA	NA
Tumour subtype, *n* (%)			
Colon	18,754 (67)	NA	NA
Proximal	9304 (33)	NA	NA
Distal	8900 (32)	NA	NA
Unspecified	550 (2)	NA	NA
Rectum	8147 (29)	NA	NA
Rectosigmoid	1220 (4)	NA	NA
Comedication*, *n* (%)			
Oral contraceptives	1200 (4)	3508 (3)	<0.0001
Hormone replacement therapy	2126 (8)	7531 (7)	<0.01
Aspirin	4847 (17)	17,420 (16)	<0.01
NSAIDs	15,965 (57)	53,531 (51)	<0.0001
Statins	7945 (28)	27,092 (26)	<0.0001
Antidiabetics	3683 (13)	11,693 (11)	<0.0001

*Defined as having a dispensation in the period before index date (i.e. ever use).
NSAID, non-steroidal anti-inflammatory drug.

Table 2 Use of levothyroxine and the risk of colorectal cancer, overall and by amount, duration, and intensity of use.

	Colorectal cancer cases, $N = 28,121$	Non-cancer controls, $N = 106,086$	OR matched (95% CI)	OR adjusted (95% CI)[†]
Never used levothyroxine	27,055 (96)	102,062 (96)		
Use of levothyroxine at any point*	1066 (4)	4024 (4)	1.00 (0.93–1.07)	0.95 (0.88–1.01)
Timing of initiation (years)				
0–≤2	249 (23)[‡]	830 (21)[‡]	1.13 (0.98–1.30)	1.12 (0.97–1.29)
>2–≤4	241 (23)[‡]	857 (21)[‡]	1.06 (0.92–1.22)	1.02 (0.88–1.18)
>4–≤6	178 (17)[‡]	787 (20)[‡]	0.85 (0.72–1.00)	0.81 (0.69–0.95)
>6–≤8	155 (15)[‡]	614 (15)[‡]	0.95 (0.80–1.14)	0.88 (0.74–1.05)
>8	134 (13)[‡]	496 (12)[‡]	0.98 (0.85–1.13)	0.89 (0.77–1.02)
Cumulative duration (years)				
>0–≤2	342 (32)[‡]	1338 (33)[‡]	0.96 (0.86–1.09)	0.94 (0.83–1.06)
>2–≤4	247 (23)[‡]	889 (22)[‡]	1.05 (0.91–1.21)	1.00 (0.87–1.15)
>4–≤6	154 (14)[‡]	686 (17)[‡]	0.85 (0.71–1.01)	0.80 (0.67–0.96)
>6	323 (30)[‡]	1111 (28)[‡]	1.10 (0.97–1.24)	1.00 (0.88–1.13)
Cumulative dose (mg)				
Unknown	3 (<0.5)[‡]	14 (<0.5)[‡]	-	-
<100	493 (46)[‡]	1964 (49)[‡]	0.95 (0.86–1.05)	0.91 (0.83–1.01)
100–<150	137 (13)[‡]	510 (13)[‡]	1.01 (0.84–1.22)	0.97 (0.80–1.17)
≥150	433 (41)[‡]	1536 (38)[‡]	1.06 (0.96–1.18)	0.98 (0.88–1.09)

[†]Adjusted for use of statins, antidiabetic, oral contraceptives, hormone replacement therapy, NSAIDs, and aspirin (ever use); *Defined as at least one dispensation of levothyroxine before index date (i.e. ever use); [‡]Percentage relative to the number of levothyroxine users.

Analysing the use of levothyroxine by cumulative dose also yielded ORs close to one.

No changes in CRC risk were found when stratifying by gender, age, and tumour stage (Fig. 1). Stratification based on CRC location revealed a modest borderline significant decreased risk in rectal cancer (OR 0.86 (95% CI 0.75–1.00)) in levothyroxine users, whereas no variations in OR for CRC in proximal and distal colon were observed. Of note, malignant neoplasms of overlapping sites of colon, unspecified sites of colon, and the rectosigmoid junction were not presented in the stratification by tumour subsite due to the low sample size of patients exposed to levothyroxine in these groups. There was a clear difference in the proportion using levothyroxine between men and women. Of all women with CRC, 7% (798 of 12,229) had used levothyroxine, compared to 2% (268 of 15,892) of all men with CRC. This difference was similar for non-cancer controls: 7% of all women (2999 of 46,461) used levothyroxine compared to 2% (1025 of 59,625) of all men. However, no difference in the risk of CRC was seen between men and women. Finally, limiting the results to long-term users of levothyroxine (use for more than 6 years) did not change the results (data not shown).

Discussion

Our study shows that there is no evidence of an association between the use of levothyroxine and the risk of CRC, even when taking into account treatment duration or dose–response relationships. These results were consistent between subgroup analyses across different age and sex groups and tumour stages. Likewise, no statistically significant risk variation was seen in the different tumour subsites. The observed differences in levothyroxine use between men and women reflect the well-known gender differences in hypothyroidism, as Hashimoto's thyroiditis is four to eight times more common in women than in men (18). Contrary to our expectation, CRC patients more often used comedication such as oral contraceptives, hormone replace therapy, aspirin, NSAIDs, statins, and antidiabetics. Those drugs potentially decrease the risk of CRC; however, this might be a reflection of cancer patients having a poorer physical health status, resulting in more comorbidities. Adjustment for these comedications only marginally changed the results.

To date, limited data on the association between levothyroxine use and CRC risk are available and have yielded conflicting results. In contrast to our study, a
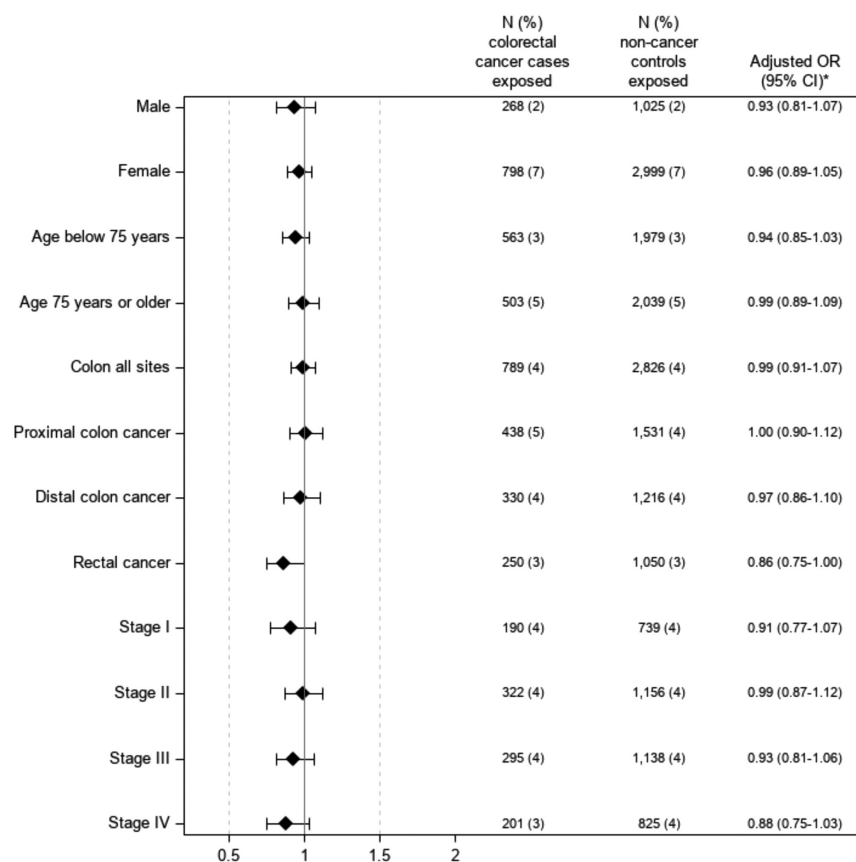

	N (%) colorectal cancer cases exposed	N (%) non-cancer controls exposed	Adjusted OR (95% CI)*
Male	268 (2)	1,025 (2)	0.93 (0.81-1.07)
Female	798 (7)	2,999 (7)	0.96 (0.89-1.05)
Age below 75 years	563 (3)	1,979 (3)	0.94 (0.85-1.03)
Age 75 years or older	503 (5)	2,039 (5)	0.99 (0.89-1.09)
Colon all sites	789 (4)	2,826 (4)	0.99 (0.91-1.07)
Proximal colon cancer	438 (5)	1,531 (4)	1.00 (0.90-1.12)
Distal colon cancer	330 (4)	1,216 (4)	0.97 (0.86-1.10)
Rectal cancer	250 (3)	1,050 (3)	0.86 (0.75-1.00)
Stage I	190 (4)	739 (4)	0.91 (0.77-1.07)
Stage II	322 (4)	1,156 (4)	0.99 (0.87-1.12)
Stage III	295 (4)	1,138 (4)	0.93 (0.81-1.06)
Stage IV	201 (3)	825 (4)	0.88 (0.75-1.03)

Figure 1
Use of levothyroxine and colorectal cancer risk by patient subgroups. *Adjusted for use of statins, antidiabetic, oral contraceptives, hormone replacement therapy, NSAIDs, and aspirin (ever use).

previous study by Rennert *et al.* found a statistically significant and inverse association between long-term levothyroxine use and CRC for women but not in men (13). However, this study used self-reported information on levothyroxine use which is subject to recall bias, especially when obtaining information going several years back. Incomplete information on levothyroxine use among CRC patients can create an artificial appearance of drug benefit. In a later study, Friedman *et al.* assessed the association with levothyroxine use for both colon cancer and rectal cancer separately and found a reduction in the risk of rectal cancer but not for colon cancer (11). In their gender-stratified analysis, this negative association between rectal cancer and levothyroxine use was statistically significant in men but not in women. In line, we also found a modestly decreased risk of rectal cancer among levothyroxine users, although this did not reach statistical significance. Another study by Boursi *et al.* found that long-term TH replacement was associated with a decreased risk of CRC (10). This protective association became stronger with cumulative duration of levothyroxine supplementation, with the highest protection given by more than 10 years of use. However, the study did not report on cumulative dosage, tumour location, or staging. In this regard, a previous study by L'Heureux *et al.* found that both hypothyroidism and hyperthyroidism were inversely associated with the risk of being diagnosed with CRC within an East Asian population cohort (12). However, after stratification for tumour location, the statistically significant association for hypothyroidism was only found for rectal cancer (adjusted OR 0.55 (0.40–0.76)) but not for colon cancer (adjusted OR 0.92 (0.74–1.16)) (12). Interestingly, in a subgroup analysis for use of levothyroxine by patients with hypothyroidism, the association between hypothyroidism and a lower risk of CRC was no longer observed (adjusted OR 0.93 (0.66–1.30)) (12). In general, evidence linking CRC onset and levothyroxine intake remains controversial as distinct studies find varying results of the use of levothyroxine and the risk of CRC.

T4 is the prohormone of the biological active triiodothyronine (T3). These pleiotropic THs play an important role in cellular metabolism, differentiation, and growth (3). The use of levothyroxine, which is a synthetic form of T4, lowers the serum (free)T3:(free)T4 ratio (19). However, circulating TH concentrations do not necessarily reflect intracellular TH bioavailability. Intracellular TH concentrations are subject to cell-specific regulation by TH transporters and the deiodinase enzymes which can activate or inactivate cellular TH, whereas type I and type II deiodinase (Dio1 and Dio2) initiate TH action by

conversion of T4 into T3. Dio3 is the inactivating enzyme and mediates the local attenuation of TH by converting T4 and T3 into the inactive metabolites rT3 and T2 (3). Importantly, Dentice *et al.* disclosed that colon adenomas and carcinomas express elevated Dio3 levels compared to surrounding normal intestinal mucosa and identified Dio3 as a transcriptional target of the Wnt/β-catenin pathway, which is aberrantly hyperactivated in almost all CRCs (7). Indeed, knockdown of β-catenin reduced Dio3 expression levels and concomitantly induced expression of Dio2, leading to a net increase of intracellular T3. These findings indicate that increased TH may reduce cell growth and enhance cell differentiation in intestinal cells. Furthermore, increased intracellular TH levels, through Dio3 depletion, significantly reduced the tumorigenic potential of colorectal stem cells (9). However, these results were obtained from rodent models and in experimental *in vitro* models using human and murine cell lines employing silencing of genes important for TH metabolism or CRC cell growth, which cannot be mimicked by extracellular TH supplementation as in the case of levothyroxine therapy (7, 20, 21). There is currently no data available on deiodinase activity in colorectal tumour biopsies from human patients. Hence, whether this protective effect also exists in humans is less clear.

Besides the ability of thyroid hormone levels to modify activity of the Wnt/β-catenin catenin pathway, T4 has also been suggested to affect carcinogenesis via an alternate signalling pathway involving the integrin αvβ3. This integrin αvβ3 acts as a cell surface receptor for T4 and to a lesser extent T3. Binding of these hormones has been shown to result in activation of rapid non-genomic signalling pathways including ERK1/2, which has stimulated cancer cell proliferation (22). This would suggest that high extracellular T4 levels are in fact carcinogenic. However, in our current data set, we find no effect of LT4 treatment on the incidence of colorectal cancer.

Our study has several important strengths. First, this study is a large population-based case–control study with 28,121 CRC cases matched to a large number of non-cancer controls. This large sample size led to a high statistical power and hence allowed us to conduct subgroup analyses on gender and age. Furthermore, by linking this database to the cancer registry, detailed information on characteristics of the colorectal tumour, including stage and subtype, could be obtained. This enabled us to study potential risk variations by tumour subsite as differences exists between the proximal and distal colon in terms of cellular origin and molecular and genetic characteristics (23). Lastly, information on

levothyroxine use was obtained from the Out-patient Pharmacy Database of the PHARMO Database Network which contains computerized dispensation records with detailed information on dosing and duration. This ensured complete and high-quality assessment of drug use.

Nonetheless, this study also had some limitations. In our study, information on biochemical markers of thyroid function (serum levels of TSH and free T4, specifically) was not available. However, it is unlikely that a large proportion of our study population had untreated overt thyroid disease during the available observation period of 7.3 years. A recent cohort study from the Netherlands showed that only 0.44% of their study population had untreated hypothyroidism, as defined by an increased serum TSH level concomitant with a low serum free T4 level (24). Although it is known that a substantial proportion of levothyroxine users appear to be undertreated (as shown by serum TSH >4.0 mE/L) (24), it is unlikely that this would skew our current findings. In fact, despite their low serum levels of free T4, undertreated levothyroxine users are still exposing their intestinal epithelium to a supraphysiological level of T4.

In an observational study, there is a potential risk of confounding bias. Although we accounted for comedication, we lacked information on other risk factors, such as smoking history, BMI, family history of cancer diagnosis at a young age, and comorbidities such as diabetes and Crohn's disease, that may influence TH levels or CRC risk. Furthermore, looking at the timing of the initiation of levothyroxine use, a modestly increased risk of CRC was seen among those starting the use of levothyroxine within 2 years before the index date. However, these findings are most likely the result of protopathic bias (e.g. early symptoms of undiagnosed cancer for which levothyroxine is prescribed) or might be explained by surveillance bias, which occurs when patients are followed up more closely than their matched controls. Finally, we have investigated the effect of levothyroxine use on CRC, which by definition also investigated the effect of Hashimoto's thyroiditis on CRC, as the majority of levothyroxine users are diagnosed with this autoimmune disease (18). To our knowledge, there is no relation between Hashimoto's thyroiditis and CRC. Finally, although being a large population study, only a small proportion (<0.1%) of the patients in the present cohort used liothyronine and could not be analysed. Since liothyronine is just recently reimbursed, we expect the number of liothyronine users to increase in the future. However, liothyronine is almost completely (95%) absorbed in the small intestines, preventing a supraphysiological

exposure of T3 to the colonic epithelium (25). Therefore, it is unlikely that liothyronine usage would affect CRC development.

In summary, we did not find an association between the use of levothyroxine and risk of CRC. However, a borderline significant risk reduction of rectal cancer was found, which is consistent with previous studies and may warrant further research. Additional evidence from both *in vivo* and prospective studies on the association between TH and CRC are needed in order to assess the implications for clinical practice.

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