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Association of Levothyroxine Sodium with Risk of Colon Cancer: A Two-Sample Mendelian Randomization Study

Lingzi L[1,2], Meixuan L[1], Siyi L[1], Jingjing L[3], Kailiang Z[1,2] and Baoping Z[1,2]**

[1]Department (Hospital) of Stomatology, Lanzhou University, China

[2]Key Laboratory of Dental Maxillofacial Reconstruction and Biological Intelligence Manufacturing, Lanzhou University, China

[3]Department of Geriatric Gastroenterology, General Hospital Southern Theatre Command Peoples Liberat, China

Abstract

Objective: Inconsistent findings have been reported in observational studies regarding the association between levothyroxine sodium and the risk of colon cancer. To mitigate potential confounding effects, we employed a Mendelian Randomization (MR) approach.

Design: Two-sample mendelian randomization analysis.

Methods: Utilizing Genome-Wide Association Studies (GWAS) datasets from the extensive UK Biobank, we conducted a two-sample Mendelian Randomization (MR) analysis to examine the causal effects of levothyroxine usage on the risk of colon cancer. We employed five different MR methods to investigate causality. The stability, heterogeneity, and pleiotropy of MR results were also evaluated.

Results: Our findings indicate a heightened risk of colon cancer in patients with levothyroxine sodium *via* the IVWFE or Multiplicative Random-Effects IVW (IVWMRE) method. The Odds Ratios (OR) were as follows: OR=1.02, p=0.169 (MR Egger); OR=1.01, p=0.072 (weighted median); OR=1.01, p=0.016 (inverse variance weighted method); OR=1.01, p=0.374 (simple mode); OR=1.01, p=0.135 (weighted mode). These results validate the selected Single Nucleotide Polymorphisms (SNPs) as appropriate genetic instruments, and confirm that the relationships between genetically predicted levothyroxine sodium usage and colon cancer risk were not confounded by potential confounders or mediators. No horizontal pleiotropy was observed in the MR analysis, and the leave-one-out analysis confirmed the stability of our results.

Conclusion: In this study, we observed an increased risk of colon cancer associated with levothyroxine use. Future research is necessary to provide more robust evidence assessing the relationship between levothyroxine and the risk of colon cancer.

Keywords: Levothyroxine; Colon cancer; Mendelian Randomization; Genome-wide association

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Correspondence:
Zhang Kailiang, Department (Hospital) of Stomatology, Lanzhou University, Lanzhou 730000, China,
Zhang Baoping, Department (Hospital) of Stomatology, Lanzhou University, Lanzhou 730000, China,

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Introduction

Primary hypothyroidism is a common illness characterized by inadequate production or metabolism of thyroid hormones, with an increasing global prevalence [1]. Levothyroxine is the initial treatment for primary hypothyroidism, consisting of hormone replacement therapy with daily oral intake of the synthetic thyroid hormone levothyroxine [2]. The majority of levothyroxine is absorbed in the upper gastrointestinal tract, with absorption rates varying from 40% to 80% [3]. Therefore, 20% to 60% of this synthetic drug is eliminated in the feces, leading to a supraphysiological exposure of the colon's outer layer to Thyroid Hormone (TH) [3]. The association between levothyroxine and several forms of cancer, such as breast cancer [4], basal cell carcinomas [5], and colon cancer has been investigated in many studies [6], including randomized controlled trials, observational studies, and meta-analyses, as levothyroxine may play a role in carcinogenesis [4-7].

Colon cancer ranks as the second most common cause of cancer-related mortality, with around 1.8 million cases diagnosed globally each year [8,9]. In colon cancer, decreased intracellular thyroid hormone levels are caused by increased activity of the TH-inactivating enzyme Deiodinase type III (Dio3) [10]. On the other hand, elevated intracellular thyroid hormone levels have been found to significantly decrease the growth rate of human colorectal tumor cell lines [11]. This prompts the question whether levothyroxine users are shielded from colon cancer development due to

supraphysiological intestinal concentrations of TH. However, prior studies have explored the association between the use of levothyroxine and the risk of colon cancer, yielding conflicting findings. Some studies found evidence for a protective effect of levothyroxine [12], while others found no association [12-15]. Furthermore, some of these studies are constrained by a small patient sample, dependence on self-reported data, and insufficient information on levothyroxine dosage, treatment duration, tumor location, and stage. Hence, a novel strategy is required to study the correlation between levothyroxine and colon cancer, in addition to the classical epidemiological method.

Mendelian Randomization (MR) is an analytical approach in which genetic variants (mostly Single Nucleotide Polymorphisms (SNPs)) are recognized as instrumental variables [16], and the random allocation of genotypes is likened to randomized trials at conception. This strategy may help decrease the impact of confounding factors and reverse causation [17]. We conducted an MR analysis using genetic "instruments" or proxies for levothyroxine to assess the causal effect of this TH on the risk of colon cancer.

Materials and Methods

Overall study design

All data were obtained from published studies approved by the institutional review boards, and informed consent was obtained from the participants of the original study [18]. Therefore, no further sanctions were required [19]. The cause-and-effect relationship between levothyroxine sodium and colon cancer was analyzed using a two-sample MR study, and Single Nucleotide Polymorphisms (SNPs) were defined as Instrumental Variables (IVs). The use of SNPs to model randomized controlled trials can help identify causal relationships between exposure characteristics (*i.e.*, levothyroxine sodium) and outcome characteristics (*i.e.*, colon cancer).

Data sources

Genetic instrument variants for exposure: Levothyroxine sodium data were obtained from the UK biobank datasets, including 13,717 cases and 323,442 controls. The study was approved by the institutional review board, and informed consent was obtained from all participants in the original study. SNPs were selected based on the following criteria: i) SNPs strongly related to levothyroxine sodium with genome-wide significance ($p<5\times10\text{-}8$). ii) Independent of each other and to avoid bias owing to Linkage Disequilibrium (LD), the LD of SNPs related to levothyroxine sodium had to fulfill $r^2<0.001$, with a window size of 10,000 kb. iii) The correlation between IV and exposure factors is typically determined using the F-statistic of the SNPs. In general, IVs with an F-statistic greater than 10 are regarded as unbiased. F-statistic = $(\beta/SE)^2$.

Study outcome: Colon cancer: Data on colon cancer were available at https://gwas.mrcieu.ac.uk/ datasets/ ukb-b-20145/ and includes 1,494 cases and 461,439 controls of European ancestry.

Statistical analysis: It is essential to consider these hypotheses to provide a valid explanation for MR analysis [20]. (i) It is well-established that IVs are strongly related to levothyroxine sodium. (ii) Colon cancer is affected only by IVs due to levothyroxine sodium defects. (iii) No confounding factors were present in the relationship between levothyroxine sodium and colon cancer according to IVs. The results can be affected by genetic variation through a single pathway rather than by separate exposure, namely horizontal pleiotropy, which contradicts the assumptions of MR and may bias the causal estimates. Three different analytical methods were used in the MR analysis to prevent this. Each analysis was based on a different horizontal multiplicity model. The benefit of comparing these three results is that the consistency of the three methods makes the results more credible. The main analysis was performed using an Inverse Variance-Weighting (IVW) approach [21], which provided the most accurate estimates but assumed that all SNPs were valid IVs. If one SNP does not meet the IVs assumption, the random-defect IVW will be used to generate a bias, which weighs each rate according to its standard error while considering possible heterogeneity. To satisfy the premise of a valid instrumental variable, the weighted median method requires at least 50% SNPs [22]. After sorting the included SNPs based on the weights, we obtained the median of the corresponding distribution function according to the results of our experiments. Additionally, if the genetic instrument does not depend on pleiotropic effects, an effect estimate can be derived from MR-Egger regression [23]. The pleiotropic effect was assessed using MR-Egger's intercept. Furthermore, a directional multiplicative effect cannot be proven if MR-Egger's intercept does not differ dramatically from zero [24].

Sensitivity analysis

Funnel plots can plot a single Wald ratio per SNP to display the directional level pleiotropy of the IVs. Nevertheless, the small number of IVs included makes it difficult to test for horizontal pleiotropy using funnel plots. The causal effect of the funnel plot was approximately symmetrical (Figure 1a). Leave-one-out analyses were performed to investigate whether estimates from IVW analyses were biased or dictated by individual SNPs, during meta-analyses that were conducted based on rerun IVW results for the remaining SNPs after omitting one SNP per succession. After removing each SNP, we performed MR analysis again systematically for the remaining SNPs. The results were consistent, indicating a significant causal relationship between the calculated results for all the SNPs (Figure 1b). In MR analysis, the second hypothesis is that SNPs inject results only by modifying the exposure of interest, without other confounding pathways. Directional multidirectionality was examined to obtain the intercept and p-value using MR-Egger regression. No horizontal pleiotropy was observed in the intercept of the MR-Egger regression ($p>0.05$), further indicating that pleiotropy did not bias the causal effect. Furthermore, in the published GWAS, there was no evidence that the included levothyroxine sodium associated SNPs were significantly associated with any phenotype except levothyroxine sodium, which indicates that the assumptions of the third MR were not violated. Consequently, there was no evidence that the genetic instruments of the 40-levothyroxine sodium-associated SNPs were significantly associated with any other phenotype on a genome-wide scale, supporting our third MR hypothesis, which is unlikely to be breached in our study [20]. The "Two sample MR" (version 0.5.6) software package was applied for MR and sensitivity analysis in R (version 4.2.1) [25].

Results

Instrumental variables for levothyroxine sodium

The SNPs' signatures of the levothyroxine sodium are shown in (Table 1). Finally, we selected 40 SNPs as the IVs. All genetic tools related to levothyroxine sodium were at a genome-wide significance level ($p<5\times10E-8$, $F>10$). The causal effects of each genetic variant on colon cancer are shown in Figures 1c, 1d.

Table 1: Summary statistics of the significant SNPs in SNP-exposure association.

	SNP	chr	pos	Effect Allele	Other Allele	beta	se	P val	eaf
1	rs10425559	19	4837487	G	A	-0.0040458	0.000492963	**0.000000000000000227**	0.600435
2	rs10748781	10	101283330	A	C	-0.00274017	0.00048554	**0.0000000167**	0.56608
3	rs10768122	11	35280852	G	A	0.00389067	0.000490039	**0.00000000000000204**	0.389156
4	rs10983700	9	100537455	C	T	0.00765655	0.000508214	**2.83E-51**	0.668654
5	rs11073337	15	38847763	C	A	0.00407069	0.000552064	**0.000000000000166**	0.251498
6	rs11571302	2	204742934	T	G	-0.00735539	0.000478934	**3.27E-53**	0.475331
7	rs11675342	2	1407628	T	C	0.00383505	0.000484084	**0.00000000000000234**	0.422209
8	rs12117927	1	236629134	A	C	0.00285914	0.00049047	**0.00000000557**	0.493528
9	rs12582330	12	103892941	T	G	-0.00352889	0.000539211	**0.0000000000598**	0.728871
10	rs1534430	2	12644736	T	C	-0.00364474	0.000490869	**0.000000000000113**	0.389593
11	rs1689510	12	56396768	C	G	0.00320014	0.000504578	**0.000000000227**	0.340713
12	rs16918198	9	101851219	A	G	0.00320486	0.000574052	**0.0000000237**	0.224222
13	rs174584	11	61610750	A	G	-0.00283532	0.000499661	**0.0000000139**	0.355186
14	rs2111485	2	163110536	G	A	0.00317162	0.000489017	**0.0000000000884**	0.609397
15	rs2412971	22	30494371	A	G	-0.00300041	0.000480781	**0.000000000436**	0.443438
16	rs2466022	8	128183646	A	T	-0.00305178	0.000487166	**0.000000000375**	0.402236
17	rs2744944	6	34658080	C	A	-0.00283726	0.000498382	**0.0000000125**	0.641213
18	rs28157	5	102595837	T	G	-0.00311142	0.000515001	**0.00000000153**	0.316822
19	rs28418426	6	32619654	C	T	0.00736767	0.000525343	**1.14E-44**	0.5296
20	rs2856822	6	33047432	C	A	-0.00609213	0.000515365	**3.09E-32**	0.312
21	rs2858483	22	37586672	C	A	0.003851	0.000484177	**0.00000000000000182**	0.423699
22	rs2921071	8	8308044	C	A	-0.00346715	0.000481142	**0.000000000000577**	0.476259
23	rs3130969	6	31065096	T	C	0.00757972	0.000500812	**9.92E-52**	0.348834
24	rs3184504	12	111884608	C	T	-0.00804286	0.00047799	**1.66E-63**	0.517816
25	rs35776863	17	7234983	A	G	0.00317529	0.000570009	**0.0000000254**	0.233122
26	rs35782497	4	187001230	A	G	-0.00313987	0.000505838	**0.00000000054**	0.34118
27	rs440674	6	29906826	G	A	-0.00462995	0.000554798	**0.0000000000000000713**	0.247615
28	rs56249713	18	67533332	C	T	-0.00265912	0.000486895	**0.0000000473**	0.420219
29	rs683763	10	89807680	T	G	0.002845	0.000511489	**0.0000000267**	0.321202
30	rs7072793	10	6106266	C	T	0.00362421	0.000485926	**0.0000000000000878**	0.410941
31	rs744253	10	6393009	G	A	0.00356615	0.000545633	**0.0000000000634**	0.740975
32	rs7582694	2	191973034	G	C	-0.00512763	0.000571878	**3.08E-19**	0.773961
33	rs7751251	6	148527798	C	T	0.00280772	0.000492306	**0.0000000118**	0.618971
34	rs853303	8	133932818	G	A	-0.00297126	0.000492415	**0.0000000016**	0.621756
35	rs9272426	6	32605189	G	A	0.00995528	0.000487751	**1.53E-92**	0.460274
36	rs9276157	6	32698369	C	T	0.00414414	0.000553211	**0.0000000000000685**	0.745634
37	rs9356551	6	167400345	C	T	-0.00466815	0.000506648	**3.17E-20**	0.334056
38	rs9507287	13	24786577	C	T	-0.00442427	0.000504093	**1.69E-18**	0.347359
39	rs9657607	9	21553641	C	G	-0.00309753	0.000513163	**0.00000000158**	0.671311
40	rs9815073	3	188115682	A	C	-0.0053748	0.000523437	**9.87E-25**	0.347569

Mendelian randomization analyses for colon cancer

We evaluated the causal relationship between levothyroxine sodium levels and colon cancer using IVW, MR-Egger, and weighted median regression (Table 2). Our findings suggest an increased risk of colon cancer in patients with levothyroxine sodium (OR=1.01; 95% CI 1.002–1.019, p=0.01).

Assessment of MR assumptions

In our study, the selection of SNPs was based on the genome-wide significance threshold of p<5×10E–8 in these analyses provided evidence for the absence of directional pleiotropy, suggesting that the second MR assumption was not violated (p=0.62). Additionally, the MR heterogeneity test showed no heterogeneity in our positive

Table 2: Conventional MR methods for the association of levothyroxine sodium levels and colon cancer.

Method	No. SNPs	β	$SE_β$	OR (95% CI)	P-value
MR Egger	40	0.015	0.011	1.016 (0.994-1.038)	0.169
Weighted median	40	0.012	0.007	1.012 (0.100-1.024)	0.072
IVW	40	0.01	0.004	1.010 (1.002-1.019)	**0.016**
Simple mode	40	0.011	0.012	1.011 (0.989-1.033)	0.374
Weighted mode	40	0.013	0.008	1.013 (0.996-1.029)	0.135

Abbreviation: MR: Mendelian Randomization; SNPs: Single-Nucleotide Polymorphisms; SE: Standard Error; OR: Odd Ratio; CI: Confidence Interval
Bold values indicate statistical significance (p<0.05)

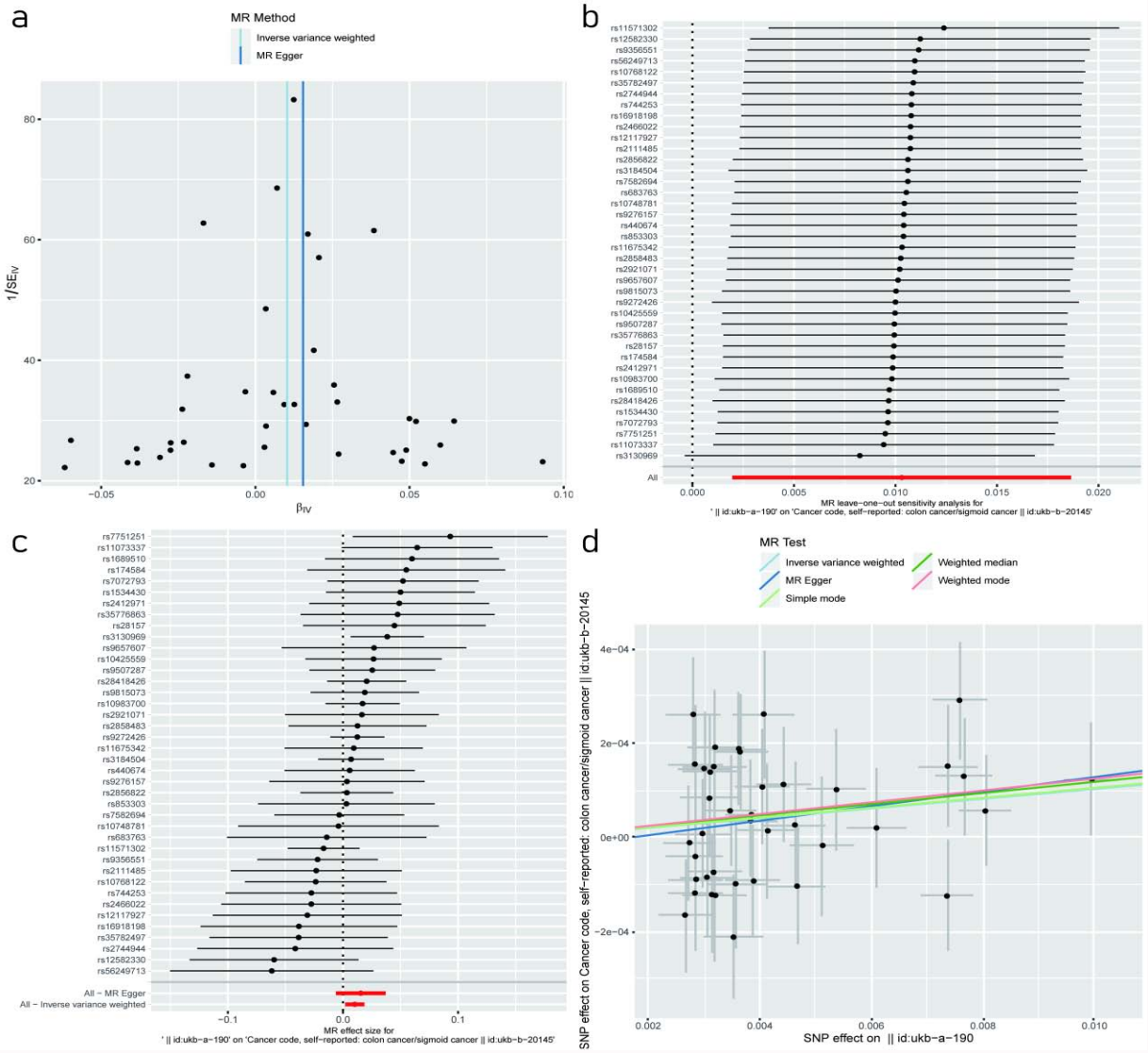

Figure 1: (a) Funnel plot showed the causal effect was approximately symmetrical. (b) Results of MR leave-one-out sensitivity analyses. (c) Forest plot of colon cancer. (d) Scatter plot of colon cancer.

outcomes (p=0.46). In summary, the rigorous assessment of the three fundamental assumptions in MR analysis was conducted in our study. The results suggested that the selected SNPs were appropriate as genetic instruments, and the relationships between genetically predicted levothyroxine sodium and colon cancer were not confounded by potential confounders or mediators.

Discussion

Our findings suggest an increased vulnerability to colon cancer in persons undergoing levothyroxine sodium medication. Previous research has investigated the link between levothyroxine use and the risk of colon cancer, yielding conflicting findings. Large population-based cohort studies have demonstrated that those who take levothyroxine are at a greater risk of developing cancer compared to non-users. This risk is particularly elevated for many types of cancer such as breast [4], endometrial, vaginal, stomach, colon [26], liver, pancreatic [27], bladder, skin, and leukemia in women, and thyroid and other endocrine cancers in men [7]. However, it reported that

untreated hypothyroidism increases the risk of breast cancer, but treating hypothyroidism with Thyroid Hormone Replacement (THR) may lower this risk. The preventive effect of this medication gets more pronounced with longer duration of therapy [28]. MR analysis indicated that hypothyroidism is causally linked to a decreased risk of lung cancer, possibly through the mediation of oxidative stress response and the PI3K/Akt signaling pathway [29]. Rennert et al. are the first to publish a report on how thyroid hormones replacement therapy can protect against the risk of colon cancer. An inverse and statistically significant connection were discovered between long-term levothyroxine use and colon cancer in women, but not in males [13]. Friedman et al. released information regarding 12,207 patients with colon cancer and 4,729 with rectum/rectosigmoid cancer in response to the study conducted by Rennert et al. [14]. Each patient was paired with 50 controls. The study found that men who took levothyroxine supplements for at least five years had a decreased incidence of rectal cancer (OR=0.66, 95% CI: 0.45–0.97, p=0.03). Reduction in the risk of colon cancer did not reach statistical significance. Postmenopausal women faced somewhat decreased risks, albeit the reduction was not statistically significant. Boursi et al. found a little increase in cancer risk in hypothyroid patients, a slight decrease in risk for patients on levothyroxine treatment, and a lower risk for patients treated for over 10 years compared to those treated for 5 to 10 years. Animal tests have confirmed that administering thyroxine can elevate the occurrence of azomethane-induced colon cancer in rats [30]. Olga Rostkowska et al.'s retrospective investigation revealed a potential link between thyroid malfunction and an increased likelihood of developing pancreatic and breast cancer, along with a heightened risk of colon cancer. In addition, thyroid hormone replacement therapy provides protection against the risk of colon cancer [12]. Levothyroxine use in population-based matched case-control studies showed a significant decrease in colon cancer risk. In population-based matched case-control studies, levothyroxine use was associated with a significantly reduced risk of colon cancer, with a statistically significant difference between male and female controls, with a strong negative association in women [28]. Estrogen and progesterone replacement therapy in peri-menopausal women has been shown to be associated with a reduced risk of colon cancer [13]. Recent research in pharmaceutical and cancer data cohorts have found that the link between hypothyroidism and a decreased risk of colon cancer is no longer present [6]. Kuiper et al. discovered that levothyroxine treatment did not provide any preventive benefits against cancers of varying duration and locations [30]. Wändell et al. investigated the potential elevated risk of both general and cause-specific cancers in individuals undergoing levothyroxine treatment [27]. They determined that levothyroxine therapy was linked to a higher incidence of cancer, particularly colon cancer, especially in women. Although the initial results were promising, there are currently fewer than 20 studies that have analyzed this subject. Hence, a more comprehensive investigation of this topic appears justified.

Thyroxine (T4) is an active precursor hormone of Triiodothyronine (T3). Levothyroxine is a synthetic form of thyroxine. Thyroid hormones exert their influence through several receptors, impacting multiple physiological pathways related to cell growth, movement, energy metabolism, cell death, immunological responses [13,31], and blood vessel formation, which can have conflicting impacts on cancer progression [28]. Thyroid hormone primarily influences biological functions *via* interacting with its nuclear receptors TRα1 and TRβ1, as well as the cell surface receptor integrin αVβ3. Thyroid hormone binding to TRα1 directly activates the expression of β-catenin, a key promoter of intestinal cell growth. In addition, integrin αVβ3 functions as a cell surface receptor for T4, triggering quick activation of the PI3K and ERK1/2 pathways, which promotes cancer cell growth and enhances angiogenesis. This suggests that high quantities of T4 outside the cells are carcinogenic [6]. TRβ1 is responsible for the anti-proliferative impact of thyroid hormone. TRβ1 expression correlates with tumor differentiation phenotype, while the absence of TRβ1 is linked to the malignant progression of human colon cancers [28]. Furthermore, the protective impact of THR on the risk of colon cancer may be linked to the activation of the estrogen pathway by thyroid hormones. T3 in breast cancer elevates estrogen receptor-alpha levels, resulting in heightened progesterone receptor levels, increased prolactin secretion, and tumor growth. Levothyroxine can influence thyroid-stimulating hormone and free T4 levels [13], perhaps providing a preventive effect against colon cancer growth in the presence of estrogen [30]. Estrogen impacts cell activity by attaching to two nuclear receptors, estrogen receptors alpha and beta. The two ER types have opposite effects on colon cancer cells. ERα activation promotes colon cancer cell proliferation through the ERK/MAPK and PI3K/AKT pathways, while ERβ activation induces apoptosis in colon malignant cells *via* the p38/MAPK pathway and caspase 3 activation. Thus, thyroid hormones can have a multitrophic impact on colon cancer progression, influenced by the interplay of many signaling pathways they trigger [28]. Within the cell, Thyroid Hormone (TH) reaches target cells by specialized plasma membrane carriers [30]. TH content is controlled by TH transporter and cell-specific deiodinase enzymes, including type I and II Deiodinase (Dio1 and Dio2), which activate TH by converting T4 to T3. Dio3, on the other hand, is an inactive enzyme. T4 and T3 are transformed into inactive metabolites to regulate the local breakdown of TH. Colonic adenomas and malignancies show increased levels of Dio3 compared to normal intestinal mucosa, and Dio3 is a transcriptional target of the Wnt/β-catenin pathway [10], as demonstrated in rodent and *in vitro* models using human and mouse cell lines. This pathway is over active in nearly all cases of colon cancer [6]. The intricate relationship between THs and cancer does not provide clear findings about whether THs promote or inhibit tumor growth [30].

Our investigation is subject to specific constraints. Firstly, most of the required data for the study was sourced from a database that did not include details on the location and stage of patients' tumors, therefore hindering the assessment of the impact of various tumor stages [28]. Retrospective data collection was conducted with recall bias [13], and information on additional risk variables such smoking history, BMI, and family history of cancer diagnosis at a young age was also missing. Furthermore, confounding biases including comorbidities such as diabetes and Crohn's disease that could impact TH levels or colon risk. Additionally, there is a lack of data regarding the dosage [13,32-34] and duration of levothyroxine use, as well as the duration of withdrawal [35]. Moreover, there is insufficient longitudinal data on thyroid function [28], particularly regarding biochemical markers like serum levels of TSH and free T4. Even when individuals using levothyroxine have low serum free T4 levels, they may still subject their intestinal epithelium to excessive levels of the hormone [6]. Finally, the appropriate usage of thyroid hormone has a significant effect on cancers and other disorders [36].

However, our work is the first to utilize three distinct analytical approaches in MR analysis. The primary analysis employs IVW methods to assess the evidence for a potential causal association

between levothyroxine use and colon cancer. Although the data do not prove a direct cause-and-effect connection between levothyroxine use and colon cancer, we have determined that persons who are treated with levothyroxine sodium are more prone to developing colon cancer. Levothyroxine is widely regarded as a safe medication for treating thyroid disorders. Patients generally adhere well to drug administration *via* the gastrointestinal route, but it is also important to take into account the specific features of the gastrointestinal tract, including the impact of drug retention and travel time [37] on drug absorption [7]. Therefore, additional meticulously planned prospective studies are required to reduce bias from observational research and make use of extensive GWAS data for MR Analysis. In the future, increased data may elucidate a greater extent of phenotypic variance, potentially offering stronger evidence for a causal link between levothyroxine and colon cancer.

Conclusion

In conclusion, the results indicate that using levothyroxine is linked to a higher risk of colon cancer, which should be considered before starting or renewing levothyroxine treatment for hypothyroid patients. We have to emphasize that this MR study specifically outlines the causative links between levothyroxine and the risks of colon cancer. Therefore, the results of the current study could serve as a reference for interested researchers to conduct further research. Further *in-vivo* investigations and meta-analyses are necessary to investigate causation and identify the mechanisms of these connections.

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References

1. Chaker L, Razvi S, Bensenor IM, Azizi F, Pearce EN, Peeters RP. Hypothyroidism. Nat Rev Dis Primers. 2022;8(1):30.
2. Hegedüs L, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, Perros P, et al. Primary hypothyroidism and quality of life. Nat Rev Endocrinol. 2022;18(4):230-42.
3. Tanguay M, Girard J, Scarsi C, Mautone G, Larouche R. Pharmacokinetics and comparative bioavailability of a levothyroxine sodium oral solution and soft capsule. Clin Pharmacol Drug Dev. 2019;8(4):521-8.
4. Wu CC, Yu YY, Yang HC, Nguyen PA, Poly TN, Islam MM, et al. Levothyroxine use and the risk of breast cancer: A nation-wide population-based case-control study. Arch Gynecol Obstet. 2018;298(2):389-96.
5. Ciavardelli D, Bellomo M, Crescimanno C, Vella V. Type 3 deiodinase: Role in cancer growth, stemness, and metabolism. Front Endocrinol. 2014;5:215.
6. Kuiper JG, Fenneman AC, van der Spek AH, Rampanelli E, Nieuwdorp M, van Herk-Sukel MPP, et al. Levothyroxine use and the risk of colorectal cancer: A large population-based case-control study. Endocrine Connections. 2022;11(1):e210463.
7. Wu CC, Islam MM, Nguyen PA, Poly TN, Wang CH, Iqbal U, et al. Risk of cancer in long-term levothyroxine users: Retrospective population-based study. Cancer Sci. 2021;112(6):2533-41.
8. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.
9. Mulcahy HE, Hyland J, O'Donoghue DP. From dinosaurs to DNA: A history of colorectal cancer. Int J Colorectal Dis. 2003;18(3):210-5.
10. Dentice M, Luongo C, Ambrosio R, Sibilio A, Casillo A, Iaccarino A, et al. β-Catenin regulates deiodinase levels and thyroid hormone signaling in colon cancer cells. Gastroenterology. 2012;143(4):1037-47.
11. Catalano V, Dentice M, Ambrosio R, Luongo C, Carollo R, Benfante A, et al. Activated thyroid hormone promotes differentiation and chemotherapeutic sensitization of colorectal cancer stem cells by regulating Wnt and BMP4 signaling. Cancer Res. 2016;76(5):1237-44.
12. Rostkowska O, Spychalski P, Dobrzycka M, Wilczyński M, Łachiński AJ, Obołończyk L, et al. Effects of thyroid hormone imbalance on colorectal cancer carcinogenesis and risk - a systematic review. Endokrynol Pol. 2019;70(2):190-7.
13. Rennert G, Rennert HS, Pinchev M, Gruber SB. A case–control study of levothyroxine and the risk of colorectal cancer. J Natl Cancer Inst. 2010;102(8):568-72.
14. Friedman GD, Schwalbe JS, Habel LA. Re: A case-control study of levothyroxine and the risk of colorectal cancer. J Natl Cancer Inst. 2011;103(21):1637-9.
15. L'Heureux A, Wieland DR, Weng CH, Chen YH, Lin CH, Lin TH, et al. Association between thyroid disorders and colorectal cancer risk in adult patients in Taiwan. JAMA Netw Open. 2019;2(5):e193755.
16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
17. Davey Smith G, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? BMJ. 2005;330(7499):1076-9.
18. Lawlor DA. Commentary: Two-sample Mendelian randomization: Opportunities and challenges. Int J Epidemiol. 2016;45(3):908-15.
19. Tan JS, Liu NN, Guo TT, Hu S, Hua L. Genetically predicted obesity and risk of deep vein thrombosis. Thromb Res. 2021;207:16-24.
20. VanderWeele TJ, Tchetgen Tchetgen EJ, Cornelis M, Kraft P. Methodological challenges in mendelian randomization. Epidemiology (Cambridge, Mass.) 2014;25(3):427-35.
21. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658-65.
22. Bowden J, Smith GD, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304-14.
23. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512-25.
24. Zhang Y, Liu Z, Choudhury T, Cornelis MC, Liu W. Habitual coffee intake and risk for nonalcoholic fatty liver disease: A two-sample Mendelian randomization study. Eur J Nutr. 2021;60(4):1761-7.
25. Broadbent JR, Foley CN, Grant AJ, Mason AM, Staley JR, Burgess S. Mendelian Randomization v0.5.0: Updates to an R package for performing Mendelian randomization analyses using summarized data. Wellcome Open Res. 2020;5:252.
26. Lu CH, Lee KD, Chen PT, Chen CC, Kuan FC, Huang CE, et al. Second primary malignancies following thyroid cancer: A population-based study in Taiwan. Eur J Endocrinol. 2013;169(5):577-85.

27. Wändell P, Carlsson AC, Li X, Sundquist J, Sundquist K. Levothyroxine treatment is associated with an increased relative risk of overall and organ specific incident cancers - A cohort study of the Swedish population. Cancer Epidemiol. 2020;66:101707.

28. Boursi B, Haynes K, Mamtani R, Yang XX. Thyroid dysfunction, thyroid hormone replacement and colorectal cancer risk. JNCI: J Natl Cancer Inst. 2015;107(6):djv084.

29. Liu W, Zhi FH, Zheng SY, Yang HS, Geng XJ, Luo HH, et al. Hypothyroidism reduces the risk of lung cancer through oxidative stress response and the PI3K/Akt signaling pathway: An RNA-seq and Mendelian randomization study. Heliyon. 2023;9(12):e22661.

30. Gagliardi F, Baldini E, Lori E, Cardarelli S, Pironi D, Lauro A, et al. Insights on the association between thyroid diseases and colorectal cancer. J Clin Med. 2023;12(6):2234.

31. Lin HY, Chin YT, Nana AW, Shih YJ, Lai HY, Tang HY, et al. Actions of l-thyroxine and Nano-diamino-tetrac (Nanotetrac) on PD-L1 in cancer cells. Steroids. 2016;114:59-67.

32. Jin J, Allemang MT, McHenry CR. Levothyroxine replacement dosage determination after thyroidectomy. Am J Surg. 2013;205(3):360-64.

33. Hemmati M, Tabesh H, Peyghambari A, Bazrafshan H. *In silico* dose adjustment of levothyroxine after total thyroidectomy using fuzzy logic methodology: A proof-of-concept study. Heliyon. 2023;9(1):e12797.

34. Miccoli P, Materazzi G, Rossi L. Levothyroxine therapy in thyrodectomized patients. Front Endocrinol. 2021;11:626268.

35. Ha TK, Kim DW, Park HK, Baek JW, Lee YJ, Park YM, et al. The effect of levothyroxine discontinuation timing on postoperative hypothyroidism after hemithyroidectomy for papillary thyroid microcarcinoma. Int J Endocrinol. 2016;2016:1-6.

36. Calissendorff J. The dangerous trend of levothyroxine medicalization. Trends Endocrinol Metab. 2023;34(12):783-5.

37. Chu JN, Traverso G. Foundations of gastrointestinal-based drug delivery and future developments. Nat Rev Gastro Hepat. 2022;19(4):219-38.