Presence of Metabolic Syndrome and Thyroid Nodules in Subjects with Colorectal Polyps

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Background: Thyroid nodules (TNs) and metabolic syndrome (MS) have been individually associated with colorectal polyps. However, the potential joint relationship between them in relation to colorectal polyps has not been fully evaluated. This study aimed to validate the association of TNs/MS and colorectal polyps/adenomas and to determine the risk of colonic polyps in patients with TNs/MS.

Material/Methods: A retrospective study was conducted on patients undergoing routine health checks in the First Affiliated Hospital of Wenzhou Medical University from July 2014 to August 2017. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for colorectal polyps/adenomas after adjusting for confounding factors. Then patients were divided into 4 groups according to whether they had TNs or MS. Relative excess risks of interaction, attributable proportion, and synergy index were used to determine the additive interaction of TNs and MS on colorectal polyps/adenomas.

Results: A total of 4514 eligible patients were included in this study. TNs and MS were confirmed to be independent risk factors for colorectal polyps/adenomas. Compared with the group of TNs(−)/MS(−), the odds ratios of TNs(+)/MS(+) in colorectal polyps (odds ratio [OR]: 3.031, 95% confidence interval [CI]: 2.262-4.062, P<0.05) or adenomas (OR: 2.894, 95% CI: 2.099-3.990, P<0.05) were significantly increased, and there was an interactive additive effect between TNs and MS.

Conclusions: TNs and MS have an associative and superimposing effect on the increased occurrence of colorectal adenomas. Colonoscopy screening should be advocated for patients with both of these diseases.

Keywords: Adenomatous Polyps • Colonic Polyps • Metabolic Syndrome X • Thyroid Nodule

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Background

Colorectal cancer is the third most commonly diagnosed of all cancers and accounts for 10.2% of cancer cases globally [1-3]. Polyps are recognized as precancerous colorectal lesions, and the incidence of colorectal cancer is higher in patients with multiple polyps [4]. Therefore, colonoscopy and endoscopic polypectomy of precancerous lesions can effectively reduce the incidence of colorectal cancer [5,6]. However, due to several factors such as limited health care resources, lack of colonoscopy screening programs, and low awareness in the population, individuals without known risk factors or symptoms usually do not undergo screening colonoscopy [7,8]. Thus, the identification of groups at high risk of developing colorectal cancer has become the focus of research. At present, adverse factors including male sex, advancing age, high waist-to-hip ratio, smoking, alcohol consumption, and metabolic syndrome (MS) have been associated with an increased risk of colorectal polyps [9-11]. Among these, the potentiating effect of MS on the occurrence of colorectal polyps and carcinogenesis may be related to inflammation, insulin resistance, and oxidative stress [12,13].

In addition, the detection rate of thyroid nodules (TNs) is higher than before, ranging from 13% to 68% by general physical examination [14,15]. In 2012, Duran et al [16] first associated colonic polyps with a higher detection rate of TNs. Subsequently, another study also demonstrated this association and reported other common mechanisms in the development of these 2 diseases in addition to insulin resistance and hyperinsulinemia [17]. These reports lead to the postulation that TNs and MS may increase the prevalence of colonic polyps.

This study aimed to further validate the association of TNs/MS and colorectal polyps adenomas and to determine the risk of colonic polyps in patients with TNs/MS.

Material and Methods

Diagnostic Criteria

All patients included in this study underwent a complete colonoscopy (examination accomplished to the ileocecal valve) performed by an experienced endoscopist, with each examination being more than 6 min. Polyethylene glycol electrolyte solution (3 L) was used for intestinal preparation before colonoscopy. During the examination, the quality of the intestinal preparation was scored, and those with poor quality were excluded from this study. All lesions identified were sampled by biopsy.

Study Design

Patients undergoing colonoscopy at the Medical and Health Care Center of the First Affiliated Hospital of Wenzhou Medical University from July 2014 to August 2017 were selected. Data on patients’ medical history, medication, physical examination, and laboratory investigations were collected in an anonymized manner. The exclusion criteria were (1) malignant tumor (including colorectal or other organs); (2) other thyroid diseases except for TNs (including thyroidectomy); (3) incomplete bowel preparation or poor quality; (4) organic bowel disease; (5) incomplete sample data; (6) mental illness (including epilepsy); (7) no history of using antidiabetic medication, including metformin, pioglitazone, and so forth. This study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University. The requirement for informed consent was waived due to the observational, retrospective nature of the study.

Measurements

On the morning of the colonoscopy procedure, the height and weight of the patient in an unlined garment were measured by a well-trained nurse. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Blood pressure was measured by using the automatic instrument with the cuff flushed to the left atrium after the patient rested for 15 min. Each patient’s past medical history, history of tobacco and alcohol consumption, and medication/drug use were obtained in the form of a questionnaire. Laboratory tests included results for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), thyrotropin, free thyroxine, free triiodothyronine, fasting plasma glucose, 2-h plasma glucose, uric acid, serum creatinine, alanine aminotransferase, and aspartate aminotransferase.

Definition of TNs and MS

Based on the clinical guidelines of the Diabetes Society of Chinese Medical Association in 2004, MS was diagnosed when 3 or more of the following components were present: infertility; BMI ≥25 kg/m²; dyslipidemia, with total cholesterol ≥1.70 mmol/L and/or HDL-C <0.90 mmol/L (male) HDL-C <1.00 mmol/L (female); high blood pressure, with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and/or using antihypertensive drugs; hyperglycemia, with fasting plasma glucose ≥6.1 mmol/L or 2-h plasma glucose ≥7.8, and/or use of hypoglycemic drugs.

For diagnosing TNs, thyroid ultrasound examination was performed by well-qualified and experienced radiologists. Moreover, thyroid ultrasonography was carried out within 1 month of colonoscopy.
Statistical Analysis

Data were analyzed by using SPSS version 22.0. Continuous variables of normal distribution were described as mean and 95% confidence intervals (CIs) and analyzed with an independent sample t test, while nonnormal distribution variables were analyzed with the Mann-Whitney U test. For data with skewed distribution, continuous variables were displayed as the 25th percentile, the median, and the 75th percentile. A chi-square test was used to analyze qualitative data. Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for colorectal polyps after adjusting for confounding factors. To further investigate the interactions between TNs and MS on colorectal polyps, the patients were divided into 4 groups: G1, TNs(–)/MS(–); G2, TNs(+)/MS(–); G3, TNs(–)/MS(+); and G4, TNs(+)/MS(+). The relative risks and 95% CIs of the 4 groups were obtained by logistic analyses. The Excel table compiled by Andersson et al [18] was used in our study to evaluate the additive effect of TNs and MS on colorectal polyps, with relative excess risks of interaction (RERI) and an attributable proportion (AP) >0 and a synergy index (SI) >1 indicating a biological interaction between the 2 conditions [19]. Subjects were also divided into several subgroups (including the type, size, and number of polyps) for stratified analyses, and the relative risks and 95% CIs were obtained.

Results

Baseline Features

A total of 4514 subjects were included in this study and divided into 2 groups according to whether polyps or adenomas were identified under colonoscopy. Colorectal polyps were discovered in 1379 patients (30.5%), and among these patients, 674 (14.9%) were found to have colorectal adenomas (Tables 1, 2). Comparisons based on patient demographics revealed that patients with colorectal polyps or adenomas were predominantly male and had higher frequencies of TNs and MS, and a higher propensity for smoking or drinking alcohol. In addition, patients with polypos/adenomas were older and had higher values for BMI, total cholesterol, triglycerides, fasting plasma glucose, HDL-C, uric acid, serum creatinine, alanine aminotransferase, and aspartate aminotransferase, while their LDL-C levels were lower than those of patients without polyps/adenomas. All of these differences were statistically significant (P<0.05).

In regression analyses, multivariate analysis revealed that age (1.049 [95% CI: 1.042-1.057], P<0.05), sex (1.767 [95% CI: 1.398-2.233], P<0.05), BMI (1.049 [95% CI: 1.021-1.077], P<0.05), HDL-C (0.689 [95% CI: 0.476-0.996], P<0.05), smoking (1.670 [95% CI: 1.412-1.976], P<0.05), TNs (1.221 [95% CI: 1.005-1.413], P<0.05), and MS (1.343 [95% CI: 1.082-1.665], P<0.05) were all independent risk factors of colorectal polyps, as shown in Table 1. When subjects with adenomatous polyps only were analyzed, multivariate analysis revealed that age (1.055 [95% CI: 1.045-1.065], P<0.05), sex (1.787 [95% CI: 1.333-2.395], P<0.05), smoking (1.302 [95% CI: 1.060-1.599], P<0.05), TNs (1.206 [95% CI: 1.060-1.445], P<0.05), and MS (1.312 [95% CI: 1.013-1.700], P<0.05) were also independent risk factors, as shown in Table 2.

Interaction Between TNs and MS

With G1 [TNs(–)/MS(–)] as the control group, and after adjusting for risk factors including sex and smoking, the incidence of colorectal polyps or colorectal adenomas in the other 3 groups [G2: TNs(+)/MS(–), G3: TNs(–)/MS(+), G4: TNs(+)/MS(+)] was significantly higher, as shown in Table 3 (P<0.05).

When the interactive and the additive effects of TNs and MS on colorectal polyps were analyzed, the RERI, AP, and SI were 0.831 (95% CI: –0.097 to 1.760), 0.274 (95% CI: 0.033-0.516), and 1.693 (95% CI: 0.988-2.900), respectively. Given that the confidence interval of RERI included 0 and the confidence interval of SI included 1, these findings suggest the absence of a combined effect of TNs and MS on the occurrence of colorectal polyps. However, in subjects confirmed as having colorectal adenomas, the RERI, AP, and SI were 1.111 (95% CI: 0.169-2.054), 0.384 (95% CI: 0.154-0.614), and 2.418 (95% CI: 1.185-4.934), as shown in Figure 1. This outcome indicated a cross-additive and potentiating effect of TNs and MS on the occurrence of colorectal adenomas, and 38.4% of colorectal adenomas were associated with the superimposition of the 2 conditions.

Stratified Analysis

To determine the effects of TNs and MS on the types (non-polyps, nonadenomatous polyps, and adenomatous polyps), numbers (1, ≥2), and sizes (<5 mm, 5-10 mm, and ≥10 mm) of colorectal polyps, subjects were analyzed by stratification, as shown in Table 4. Compared with G1, the odds ratio (OR) of G4 was significantly higher in nonadenomatous polyps, adenomatous polyps, polypos number=1, polypos number ≥2, polypos size <5 mm and 5-10 mm (P<0.05). Furthermore, subjects in G2 had a higher OR in all types, numbers, and sizes of colorectal polyps (P<0.05), while subjects in G3 had a higher OR in nonadenomatous polyps, adenomatous polyps, polypos number=1, polypos number ≥2, and polypos size <5 mm (P<0.05).

Discussion

TNs and MS have been demonstrated to be independently related to an increased prevalence of colonic polyps. Several
### Table 1. Baseline features and independent risk factors in colorectal polyps.

| Basic information | Polyps (1379) | Non-polyp (3135) | P value | Univariate analysis | Multivariate analysis |
|-------------------|---------------|------------------|---------|--------------------|-----------------------|
| Age (years)       | 50 (44-57)    | 45 (39-52)       | 0.000   | 2.311 (2.008-2.661) | 0.000 1.049 (1.042-1.057) |
| Sex (Male)        | 1033(74.9)    | 1767(56.4)       | 0.000   | 1.048 (1.041-1.055) | 0.000 1.767 (1.398-2.233) |
| BMI (kg/m²)       | 24.5(±3.1)    | 23.3 (21.2-25.5) | 0.000   | 1.114 (1.091-1.137) | 0.000 1.049 (1.042-1.057) |
| TC (mmol/L)       | 5.31 (4.68-6.00) | 5.2 (4.6-5.9)    | 0.003   | 1.082 (1.020-1.147) | 0.009 1.138 (0.886-1.462) |
| TG (mmol/L)       | 1.61 (1.10-2.38) | 1.32 (0.94-2.05) | 0.000   | 1.094 (1.049-1.140) | 0.000 0.905 (0.815-1.004) |
| HDL-C (mmol/L)    | 1.18 (1.02-1.40) | 1.27 (1.08-1.51) | 0.000   | 0.446 (0.363-0.549) | 0.000 0.689 (0.476-0.996) |
| LDL-C (mmol/L)    | 3.20 (2.67-3.79) | 3.10 (2.61-3.67) | 0.001   | 1.128 (1.047-1.215) | 0.001 0.885 (0.668-1.172) |
| TSH (mIU/L)       | 1.54 (1.10-2.22) | 1.64 (1.14-2.41) | 0.005   | 0.925 (0.878-0.975) | 0.004 0.954 (0.909-1.001) |
| FT<sub>3</sub> (pmol/L) | 11.1 (10.2-12.3) | 11.2 (10.2-12.3) | 0.562   | 0.997 (0.972-1.022) | 0.787 – – |
| FT<sub>4</sub> (pmol/L) | 5.0 (4.5-5.4) | 5.0 (4.5-5.4) | 0.971   | 1.016 (0.956-1.080) | 0.617 – – |
| FPG (mmol/L)      | 4.8 (4.3-5.2) | 4.7 (4.2-5.1)    | 0.000   | 1.182 (1.120-1.248) | 0.000 1.129 (0.968-1.193) |
| UA (mmol/L)       | 353 (298-415) | 331 (271-391)    | 0.000   | 1.003 (1.002-1.004) | 0.000 1.000 (0.999-1.001) |
| Scr (umol/L)      | 70 (60-78)    | 65 (55-75)       | 0.000   | 1.020 (1.016-1.020) | 0.000 1.000 (0.993-1.007) |
| ALT (U/L)         | 24 (17-37)    | 22 (16-33)       | 0.000   | 1.004 (1.002-1.006) | 0.001 1.001 (0.996-1.005) |
| AST (U/L)         | 25 (20-31)    | 24 (20-29)       | 0.000   | 1.005 (1.002-1.009) | 0.006 1.000 (0.993-1.007) |
| Smoking n (%)     | 542(39.3)     | 738(23.5)        | 0.000   | 2.103 (1.836-2.410) | 0.000 1.670 (1.412-1.976) |
| Alcohol n (%)     | 601(43.6)     | 1050(33.5)       | 0.000   | 1.534 (1.347-1.746) | 0.000 0.998 (0.849-1.172) |
| TNs n (%)         | 542(39.3)     | 1035(33.0)       | 0.000   | 1.314 (1.152-1.498) | 0.000 1.221 (1.005-1.413) |
| MS n (%)          | 277(20.1)     | 340(10.8)        | 0.000   | 2.066 (1.738-2.457) | 0.000 1.343 (1.082-1.665) |

ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; FPG – fasting plasma glucose; FT<sub>3</sub> – free triiodothyronine; FT<sub>4</sub> – free thyroxine; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; MS – metabolic syndrome; OR – odds ratio; Scr – serum creatinine; TC – total cholesterol; TG – triglyceride; TNs – thyroid nodules; TSH – thyrotropin; UA – uric acid.
| Basic information | Adenomas (1379) | Non-adenoma (3135) | P value | Univariate analysis | Multivariate analysis |
|-------------------|-----------------|-------------------|---------|-------------------|---------------------|
|                   | Age (years)     |                   |         |                   |                     |
|                   | 52 (45-59)      | 46 (40-53)        | 0.000   | 1.053 (1.045-1.062) | 0.000 (1.045-1.065) |
|                   | Sex (Male)      |                   |         |                   |                     |
|                   | 507 (75.2)      | 2293 (59.7)       | 0.000   | 2.048 (1.700-2.468) | 1.787 (1.333-2.395) |
|                   | BMI (kg/m²)     |                   |         |                   |                     |
|                   | 24.4 (3.1)      | 23.5 (21.4-25.7)  | 0.000   | 1.083 (1.056-1.112) | 0.000 (1.028-1.065) |
|                   | TC (mmol/L)     |                   |         |                   |                     |
|                   | 5.35 (4.67-6.07)| 5.21 (4.60-5.92)  | 0.018   | 1.079 (1.002-1.163) | 0.044 (0.684-1.286) |
|                   | TG (mmol/L)     |                   |         |                   |                     |
|                   | 1.19 (1.03-1.42)| 1.25 (1.06-1.48)  | 0.000   | 0.619 (0.475-0.806) | 0.000 (0.685-1.718) |
|                   | HDL-C (mmol/L)  |                   |         |                   |                     |
|                   | 3.25 (±0.88)   | 3.11 (2.62-3.69)  | 0.038   | 1.101 (1.001-1.210) | 0.048 (0.763-1.548) |
|                   | MS n (%)        |                   |         |                   |                     |
|                   | 274 (40.7)      | 1303 (33.9)       | 0.001   | 1.334 (1.128-1.577) | 0.001 (1.066-1.445) |
|                   | Fasting Plasma Glucose (mg/dL) |           |         |                   |                     |
|                   | 97 (59-117)     | 112 (90-140)      | 0.000   | 1.019 (1.001-1.037) | 0.000 (0.998-1.015) |

ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; FPG – fasting plasma glucose; FT₃ – free triiodothyronine; FT₄ – free thyroxine; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; MS – metabolic syndrome; OR – odds ratio; Scr – serum creatinine; TC – total cholesterol; TG – triglyceride; TNs – thyroid nodules; TSH – thyrotropin; UA – uric acid.
studies have reported a higher prevalence of colorectal adenoma in patients with MS [12,20,21], but the molecular mechanisms remain to be delineated. Given that MS usually develops as a result of overconsumption of food, some studies have postulated that excessive energy intake exceeds the storage capacity of adipose and muscle tissue, leading to metabolic stress. This then activates inflammatory signaling cascades and increases the production of cytokines, causing chronic low-grade inflammation in the body and resulting in insulin resistance [22,23]. Furthermore, insulin resistance and increased insulin levels lead to an increase in the levels of free insulin-like growth factor-1 (IGF-1) and a decrease in insulin-like growth factor binding proteins-3 (IGFBP-3) [24]. These alterations may mimic the dynamic imbalance of growth hormone and IGF1, which may potentiate the development of precancerous lesions such as colorectal adenomas [25].

In the study by Duran et al [16], the incidence of TNs was significantly higher in patients with colorectal polyps, which were significantly associated with age, BMI, metabolism-related diseases, and so forth [26]. Insulin resistance has also been considered to affect the pathogenesis of TNs [27-29]. Other risk factors, including waist circumference, HDL, and impaired fasting blood glucose levels, have also been associated with TNs [30,31].

Moreover, evidence has revealed not only a reciprocal relationship of causality between TNs and MS but has also shown that TNs can be independent of MS and insulin in the pathogenesis of colorectal polyps through other common mechanisms [17]. This finding warrants further studies to explore an independent pathway for TNs in potentiating the development of colorectal polyps. The purpose of the current study was to verify the potential combined effects of TNs and MS.

After adjusting for confounding factors, we confirmed that TNs and MS are associated with an increased incidence of colorectal polyps/adenomas. Furthermore, the incidence of colorectal polyps or colorectal adenomas was the highest in patients with TNs and MS (OR: 3.031 and 2.894, respectively). Compared with other groups, the difference was statistically significant (P<0.05). Also, our study was the first to our knowledge to demonstrate an additive effect of TNs and MS among patients with colorectal adenoma. Compared with patients without TNs and MS, patients with both TNs and MS had a risk of colorectal adenoma that was 1.111 times higher, and the combined effect of these disorders was associated with 38.4% of patients with colonic adenomas. Therefore, these findings suggest that TNs may further increase the risk of colorectal adenomas in patients with MS.

Table 3. Interaction between thyroid nodules and metabolic syndrome.

| Group | Total number | Colorectal polyps | Colorectal adenomas |
|-------|--------------|-------------------|---------------------|
|       | Number OR (95% CI) P value | Number OR (95% CI) P value |          |
| G1    | 2528 669 1 (1.302-1.758) 0.000 | 324 1 (1.165-1.709) 0.000 |          |
| G2    | 1369 433 1.513 (1.354-2.103) 0.000 | 211 1.411 (1.165-1.709) 0.000 |          |
| G3    | 409 168 1.688 (2.62-4.062) 0.000 | 76 1.373 (1.04-1.813) 0.025 |          |
| G4    | 208 109 3.031 (2.099-3.990) 0.000 | 63 2.894 (2.099-3.990) 0.000 |          |

G1 – TNs(–)MS(–); G2 – TNs(+)MS(–); G3 – TNs(–)MS(+); G4 – TNs(+)MS(+); MS – metabolic syndrome; OR – odds ratio (adjusted for sex and smoking); TNs – thyroid nodules.

Figure 1. Relative risk with contributions from different exposure categories marked.
The stratified analysis confirmed that patients with both disorders had a higher risk of colonic polyps, especially adenomatous polyps and multiple polyps.

There were several limitations to this study. First, it was a single-center study and therefore requires validation based on multicenter data. Also, this study included a specific patient population with data on physical examination and adopted a regression analysis, which inevitably incurred a selection bias. Finally, ultrasonic imaging was used to detect TNs, but some patients might have potentially cancerous TNs and should undergo a biopsy to reduce the selection variation [32,33]. In future studies, TNs can be classified by the size and the effect of TNs on the occurrence of colonic polyps in subgroup analysis. In addition, patients with colorectal cancer can be evaluated further regarding the association with TNs and MS as risk factors in carcinogenesis.

Table 4. Stratified analysis.

|                | N1  | N2  | N3  | N4  | G1     | G2     | G3     | G4     |
|----------------|-----|-----|-----|-----|--------|--------|--------|--------|
| Polyp-free     | 1859| 936 | 241 | 99  | 1.066* | 0.592* | 0.330* |        |
|                |     |     |     |     | (0.569-0.768) | (0.475-0.738) | (0.246-0.442) |        |
| Adenomaous polyps | 324 | 211 | 76  | 63  | 1.411* | 1.373* | 2.894* |        |
|                |     |     |     |     | (1.165-1.709) | (1.040-1.813) | (2.099-3.990) |        |
| Non-adenomaous polyps | 345 | 223 | 93  | 46  | 1.389* | 1.666* | 1.732* |        |
|                |     |     |     |     | (1.151-1.675) | (1.283-2.163) | (1.220-2.458) |        |
| Number         |     |     |     |     | 1.349* | 1.628* | 1.997* |        |
|                |     |     |     |     | (1.123-1.622) | (1.255-2.110) | (1.429-2.790) |        |
| ≥2             | 313 | 202 | 76  | 57  | 1.455* | 1.387* | 2.598* |        |
|                |     |     |     |     | (1.195-1.772) | (1.048-1.836) | (1.859-3.629) |        |
| Size (mm)      |     |     |     |     | 1.372* | 1.545* | 2.043* |        |
| <5             | 441 | 278 | 110 | 64  | (1.155-1.628) | (1.209-1.973) | (1.490-2.801) |        |
| 5-10           | 194 | 121 | 47  | 39  | 1.309* | 1.395 | 2.695* |        |
|                |     |     |     |     | (1.028-1.667) | (0.993-1.960) | (1.842-3.942) |        |
| ≥10            | 34  | 34  | 11  | 6   | 2.127* | 1.790 | 2.100  |        |
|                |     |     |     |     | (1.308-3.461) | (0.897-3.574) | (0.870-5.068) |        |

N1 – number of people in group 1; N2 – number of people in group 2; N3 – number of people in group 3; N4 – number of people in group 4 (adjusted for sex and smoking). * P<0.05.

The stratified analysis confirmed that patients with both disorders had a higher risk of colonic polyps, especially adenomatous polyps and multiple polyps.

Conclusions

In conclusion, TNs and MS have been established as independent risk factors for colorectal polyps and colorectal adenomas. Meanwhile, TNs and MS have superimposed effects on the occurrence of colorectal adenomas. Therefore, patients with both TNs and MS should be offered a screening colonoscopy as a high-risk group in accordance with colonoscopy guidelines [34].

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