Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan

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ABSTRACT
Background: Although case-control studies support the idea that soy foods or isoflavone intake is associated with a decreased risk of lung cancer, little evidence is available from prospective cohort studies. Moreover, no prospective study has addressed this association in men.

Objective: We investigated the association between isoflavone intake and lung cancer incidence.

Design: We conducted a population-based prospective cohort study in 36,177 men and 40,484 women aged 45–74 y with no history of cancer at baseline in 1995–1999. Participants responded to a validated questionnaire, which included 138 food items. We used Cox proportional hazards regression analysis to estimate the hazard ratios (HRs) and 95% CIs of lung cancer incidence according to isoflavone intake, which was estimated by genistein content from soy foods.

Results: During 11 y (671,864 person-years) of follow-up, we documented 481 male and 178 female lung cancer cases. In men we found an inverse association between isoflavone intake and risk of lung cancer in never smokers (n = 13,051; multivariate HR in the highest compared with the lowest quartile of isoflavone intake: 0.43; 95% CI: 0.21, 0.90; P for trend = 0.024) but not in current or past smokers. A similar, nonsignificant inverse association was seen in women (n = 38,211; HR: 0.67; 95% CI: 0.41, 1.10; P for trend = 0.135). We also tested effect modification by smoking status (P for interaction = 0.085 in men and 0.055 in men and women combined).

Conclusion: In a large-scale, population-based, prospective study in Japan, isoflavone intake was associated with a decreased risk of lung cancer in never smokers.

INTRODUCTION
Isoflavones, of which genistein and daidzein are the 2 major forms, are obtained primarily from soy or soy products in Asian diets. Because their structure is similar to that of the human female hormone 17β-estradiol, isoflavones have particular affinity for the β-estrogen receptor (1) and can therefore act as estrogen agonists and antagonists that compete for estradiol at the receptor complex (2). In fact, isoflavones have been proposed to lower the risk of several sites of cancer, such as breast (3, 4) and prostate (5, 6), that are considered hormone related.

On the basis of findings that estrogen receptors are expressed in healthy lung tissue and lung tumors (7) and that estrogen induces cell proliferation in vivo and in vitro (8), a possible role for sex hormones in lung carcinogenesis has been proposed. Furthermore, several epidemiologic studies reported that hormone replacement therapy is associated with lung cancer risk, albeit that the direction of the association was not consistent (9–12). Thus, isoflavone intake may be related to the risk of lung as well as other hormone-related cancers.

Although 8 case-control studies in Asian populations on the association between soy foods or isoflavone intake and lung cancer risk (13–19) have been reported, the association remains controversial, particularly with regard to subgroup analyses by sex, smoking status, or histologic type. Moreover, little evidence is available from prospective cohort studies in Asia (20), and no prospective study has addressed this association in men. Recent observations suggest that lung cancer in never smokers is a distinct entity (21), and sex differences in lung cancer susceptibility have been debated (22). Given this background, prospective investigation of the association of isoflavone intake with lung cancer risk by smoking status and sex would be informative.

We investigated the association between isoflavone intake and lung cancer risk among Japanese men and women on the basis of a large-scale, population-based, prospective study with an 11-y follow-up period.

SUBJECTS AND METHODS
Study population
The Japan Public Health Center–based Prospective Study was launched during 1990–1994. We defined the study population as all registered Japanese inhabitants in 11 public health...
center (PHC) areas aged 40–69 y at the start of the baseline survey (23) (n = 140,420). The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan. For the present analysis, we excluded 2 PHC areas (Tokyo and Osaka) because data on cancer incidence were not available and a different definition of study population was used in Tokyo and Osaka, respectively (n = 23,524).

Participants in the present study were those aged 45–74 y who responded to a self-administered 5-y follow-up questionnaire, which included demographic data, personal medical history, smoking and alcohol drinking, diet (via a food-frequency questionnaire [FFQ]), and other lifestyle factors in 1995–1999. We initially identified 116,672 participants as the study population at the baseline survey after exclusion of 224 participants who were found to be ineligible due to non-Japanese nationality (n = 51), late report of emigration that occurred before the start of the follow-up period (n = 166), incorrect birth date (n = 3), and duplicate registration (n = 4). Furthermore, we excluded the 1631 participants who had died, moved out of the study area, or were lost to follow-up before the 5-y follow-up questionnaire survey. The remaining 115,041 participants were considered eligible for the present study. A total of 91,239 responded to the questionnaire, which gave a response rate of 79%.

We then excluded participants with incomplete information on soy food intake (n = 1115), those who reported daily energy intakes at the upper or lower 2.5% ends of the range (980 and 4222 kcal for men and 826 and 3693 kcal for women, respectively) (n = 4504), and those with incomplete information on smoking status (n = 5807). We also excluded 3152 participants who reported or were diagnosed with cancer before the 5-y follow-up questionnaire survey. Finally, a total of 76,661 participants (36,177 men and 40,484 women) were included in the analysis.

Exposure data

The FFQ used in the 5-y follow-up questionnaire survey was designed to estimate dietary intake from 138 food items and was validated for the estimation of various nutrients and food groups. The participants were asked about how often they consumed the individual food items (frequency of intake) and representative relative sizes compared with standard portions during the previous year (24). Of the 138 food items, 8 items (standard portion size) dealt specifically with consumption of soy and isoflavones: miso soup (150 g), soymilk (200 g), tofu for miso soup (20 g), tofu for other dishes (75 g), yushidofo (predrawn tofu; 150 g), koyadofu (freeze-dried tofu; 60 g), aburaage (deep-fried tofu; 2 g), and natto (fermented soybeans; 50 g). These 8 items contributed 95.9% of total genistein intake in the estimates from dietary records in our validation study (25).

For miso soup, the FFQ included questions on the frequency of consumption (almost never, 1–3 d/mo, 1–2 d/wk, 3–4 d/wk, 5–6 d/wk, or daily) and on the daily amount consumed (number of bowls: <1, 1, 2, 3, 4, 5, 6, 7–9, or 10). For soymilk, the FFQ included questions on 10 frequency categories only: almost never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 glass/d, 2–3 glasses/d, 4–6 glasses/d, 7–9 glasses/d, or >9 glasses/d. For other soy foods, the FFQ contained questions on frequency (almost never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–6 times/d, or ≥7 times/d) and sizes relative to a standard portion (small [50% smaller than standard], medium [same as standard], or large [50% larger than standard]).

Daily intake of each food item was calculated by multiplying frequency by standard portion and, if available, the relative portion size for each item in the FFQ. Intake of genistein and daidzein was calculated by using values in a specially developed food composition table of Japanese foods (26), which contained measured values of soy foods (27, 28). This allowed for the effect of food processing on genistein content, including fermentation, to be taken into consideration in estimating intake. We did not collect information on the use of isoflavone supplements. Intake of food and nutrients was log-transformed and adjusted for total energy intake by the residual model (29). Because the estimates of genistein and daidzein intake were highly correlated (Spearman’s rank correlation coefficient = 0.996), the results for genistein are provided as representative for isoflavones.

To evaluate the validity and reproducibility of energy-adjusted genistein intake, we compared the estimates from the FFQ with 28-d (or 14-d for the Ishikawa PHC area) dietary records and with the FFQ (1-y interval), respectively, obtained from a sub-sample of the cohort (6, 30–32). Spearman’s rank correlation coefficients were 0.65 (cohort I) and 0.48 (cohort II) in men and 0.55 (cohort I) and 0.45 (cohort II) in women for validity and 0.75 (cohort I) and 0.51 (cohort II) in men and 0.69 (cohort I) and 0.41 (cohort II) in women for reproducibility. Moreover, Spearman’s rank correlation coefficient for genistein between energy-adjusted intake from the FFQ, from serum concentration was 0.22, and from creatinine-adjusted urinary excretion was 0.30 (25).

Follow-up

We followed study participants until 31 December 2005. Participants who died or moved to other municipalities were identified annually through residential registers in the respective PHC areas. Cause of death was confirmed by using mortality data from the Ministry of Health, Labor, and Welfare. Among study participants, 6027 (7.9%) died, 2781 (3.6%) moved away, and 248 (0.3%) were lost to follow-up during the study period.

We identified lung cancer incidence by voluntary reports from local major hospitals in the study areas, and data linkage with population-based cancer registries, with permission. We used death certificate information as a supplementary information source. In our cancer registry system, the proportion of cases for which information was obtained from death certificates only was 4.7% during the study period. During 671,864 person-years of follow-up (median follow-up period: 8.0 y), a total of 659 (481 in men and 178 in women) newly diagnosed lung cancer cases were identified.

The site of origin and histologic type were coded by using the International Classification of Diseases for Oncology, Third Edition (C34.0–C34.9) (33). Diagnosis of lung cancer was confirmed by histologic or cytologic examination in 84% of cases (n = 556) and was based on clinical findings or unspecified evidence in the remaining 16% of cases. Histologic type was classified into adenocarcinoma (n = 289; 44%), squamous cell carcinoma (n = 144; 22%), small cell carcinoma (n = 71; 11%), and other histologic types according to the World Health Organization’s histologic classification of lung tumors (34).
Statistical analysis

We prospectively counted the number of person-years of follow-up for each participant from the date of completion of the 5-y follow-up questionnaire until the date of diagnosis of lung cancer, date of death, movement out of the study area, or 31 December 2005, whichever occurred first.

Cox proportional hazards regression analysis was used to calculate the hazard ratios (HR) and 95% CIs of lung cancer incidence according to quartile of isoflavone intake and to adjust for potentially confounding variables by using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC) (35). Dummy variables were created for quartiles of isoflavone intake, and the lowest quartile used as the reference category. We calculated \( P \) values for the analysis of linear trends by assigning ordinal values for categories of isoflavone intake and entering the number as a continuous term in the regression model. All reported \( P \) values are 2-tailed.

Multivariate-adjusted HRs were adjusted for age (in y), study area (9 PHC areas), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or \( \geq 40 \) cigarettes/d in men and <20 or \( \geq 20 \) cigarettes/d in women), and alcohol consumption (non-drinker; current drinker: 1–150, 151–300, 301–450, or \( \geq 451 \) g ethanol/wk in men and non-drinker or current drinker in women), menopausal status in women (premenopausal, natural, or induced postmenopausal), and total intake of vegetables, fruit, and fish (quarters). We did not include use of exogenous female hormones as a covariate because we identified only 2 lung cancer cases in current users of exogenous female hormones.

We conducted stratified analysis by smoking status on the association between isoflavone intake and lung cancer risk. We then tested effect modification by smoking status through the addition of cross-product terms to the multivariate model. Among never smokers, we performed additional analyses by using information on passive smoking or age at menarche in the baseline survey because the 5-y follow-up questionnaire did not include these questions. For age at menarche, we included combined categories of age at menarche (<16 or \( \geq 16 \) y old) and menopause (\( \leq 50 \) or \( >50 \) y old) in the multivariate model among never-smoking postmenopausal women on the basis of our previous finding (10). All analyses were repeated after the exclusion of participants diagnosed in the first 3 y of follow-up.

RESULTS

The characteristics of participants according to isoflavone intake are shown in Table 1. Those with higher intakes were less likely to be current smokers and more likely to be postmenopausal and to consume more vegetables, fruit, and fish.

The association between isoflavone intake and risk of lung cancer is shown in Table 2. We found no significant association in men or women, although the point estimates of multivariate-adjusted HRs in the highest quintile of isoflavone intake were below unity. After adjustment for age, study area, smoking status, alcohol consumption, menopausal status in women, and total vegetable, fruit, and fish intake, the multivariate HRs of lung cancer for the highest compared with the lowest quartile of isoflavone intake were 0.89 (95% CI: 0.67, 1.19; \( P \) for trend = 0.451) in men and 0.83 (95% CI: 0.54, 1.29; \( P \) for trend = 0.409) in women.

The results of stratified analysis by smoking status on the association of isoflavone intake with lung cancer risk are shown in Table 3. In men, an inverse association was found among...
never smokers (multivariate HR for the highest compared with the lowest quartile: 0.43; 95% CI: 0.21, 0.90; \( P \) for trend = 0.024), whereas no association was found among current or past smokers. In women, the corresponding HR among never smokers was 0.67 (95% CI: 0.41, 1.10; \( P \) for trend = 0.135). We were unable to show an association in current and past smoking women because of the small number of lung cancer cases (\( n = 17 \) and 4, respectively). We also tested effect modification by smoking status on the association between isoflavone intake and lung cancer risk among men (\( P \) for interaction = 0.085) and men and women combined (\( P \) for interaction = 0.055).

Our analyses on the association of individual soy foods with lung cancer risk in never smokers showed similar a direction to that of the association with total isoflavone intake: the

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Age- and study area– and multivariate-adjusted hazard ratios (HRs) for lung cancer incidence according to intake of isoflavones (( n = 76,661 ))¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile of isoflavone intake</td>
<td></td>
</tr>
<tr>
<td>Men (( n = 36,177 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>117</td>
</tr>
<tr>
<td>Person-years</td>
<td>76,442</td>
</tr>
<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Women (( n = 40,484 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>49</td>
</tr>
<tr>
<td>Person-years</td>
<td>87,644</td>
</tr>
<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

¹ A Cox proportional hazards model was used to estimate HRs and 95% CIs. Results for isoflavone are reported in terms of those for genistein because of the high correlation between intake estimates for genistein and daidzein.

² Adjusted for age (in y), study area (9 public health center areas), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d in men and <20 or ≥20 cigarettes/d in women), alcohol consumption (nondrinker; current drinker: 1–150, 151–300, 301–450, or ≥451 g ethanol/wk in men and nondrinker or current drinker in women), menopausal status in women (premenopausal, natural, or induced postmenopausal), and total intake of vegetables, fruit, and fish (quartiles).

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Age- and study area– and multivariate-adjusted hazard ratios (HRs) for lung cancer incidence according to intake of isoflavones by smoking status¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile of isoflavone intake</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Never smokers (( n = 13,051 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>22</td>
</tr>
<tr>
<td>Person-years</td>
<td>26,234</td>
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<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Current smokers (( n = 16,792 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>74</td>
</tr>
<tr>
<td>Person-years</td>
<td>38,012</td>
</tr>
<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Past smokers (( n = 6334 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>21</td>
</tr>
<tr>
<td>Person-years</td>
<td>12,195</td>
</tr>
<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Never smokers (( n = 38,211 ))</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>43</td>
</tr>
<tr>
<td>Person-years</td>
<td>81,395</td>
</tr>
<tr>
<td>Age- and area-adjusted HR (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Multivariate-adjusted HR² (95% CI)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

¹ A Cox proportional hazards model was used to estimate HRs and 95% CIs. Results for isoflavone are reported in terms of those for genistein because of the high correlation between intake estimates for genistein and daidzein.

² Adjusted for age (in y), study area (9 public health center areas), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d in men and <20 or ≥20 cigarettes/d in women), alcohol consumption (nondrinker; current drinker: 1–150, 151–300, 301–450, or ≥451 g ethanol/wk in men and nondrinker or current drinker in women), menopausal status in women (premenopausal, natural, or induced postmenopausal), and total intake of vegetables, fruit, and fish (quartiles).
multivariate HRs of the highest compared with lowest quartile of intake were 0.89 (95% CI: 0.45, 1.75; \( P \) for trend = 0.860) in men and 0.85 (95% CI: 0.54, 1.36; \( P \) for trend = 0.575) in women for miso soup, 0.66 (95% CI: 0.33, 1.31; \( P \) for trend = 0.197) in men and 0.95 (95% CI: 0.59, 1.53; \( P \) for trend = 0.831) in women for tofu, and 0.95 (95% CI: 0.45, 2.02; \( P \) for trend = 0.562) in men and 0.81 (95% CI: 0.48, 1.37; \( P \) for trend = 0.450) in women for natto.

We also investigated the association between isoflavone intake and risk of lung cancer by histologic type among never smokers. Because we did not have a sufficient number of lung cancer cases to analyze individual histologic types \[\text{adenocarcinoma (}\ n = 33; 45\%\text{), squamous cell carcinoma (}\ n = 16; 22\%\text{), and small cell carcinoma (}\ n = 5; 7\%\text{) in men; adenocarcinoma (}\ n = 115; 73\%\text{) and squamous cell carcinoma (}\ n = 10; 6\%\text{) in women}\], we show the results of adenocarcinoma in women only: the multivariate HR for the highest compared with the lowest quartile among never-smoking women was 0.76 (95% CI: 0.42, 1.37; \( P \) for trend = 0.386).

We conducted additional analyses among never smokers. When analysis was restricted to participants who were not exposed to passive smoking at the workplace (4493 participants with 25 lung cancer cases in men; 22,499 participants with 96 lung cancer cases in women), similar results were obtained (multivariate HR for the highest compared with the lowest quartile: 0.68; 95% CI: 0.21, 2.20; \( P \) for trend = 0.257 in men; multivariate HR: 0.56; 95% CI: 0.30, 1.05; \( P \) for trend = 0.087 in women). In postmenopausal women, further adjustment with the use of combined categories of age at menarche and menopause did not alter the results substantially (data not shown). Results after the exclusion of cases diagnosed in the first 3 y of follow-up were essentially unchanged (data not shown).

**DISCUSSION**

In this population-based prospective cohort study, we found an inverse association between isoflavone intake and risk of lung cancer in never-smoking men but not in current- or past-smoking men. We saw a similar decrease in risk in never-smoking women. Our findings support the possibility of effect modification by smoking status on the association between isoflavone intake and lung cancer risk (\( P \) for interaction = 0.085 in men and 0.055 in men and women combined). To our knowledge, this is the first prospective cohort study to report the association between isoflavone intake and lung cancer in men.

Several in vitro and in vivo studies have supported a protective effect of isoflavones on lung carcinogenesis. Lian et al (36) reported that genistein inhibited cell growth and induced apoptosis in non–small cell lung cancer cells. In female athymic mice, soy phytochemicals slowed the in vivo growth of non–small cell xenografts (37).

In previous studies in Asian countries, case-control studies have also suggested a protective effect of soy foods or isoflavone intake against lung cancer incidence (13, 15–19). With regard to prospective studies, however, only one study has been reported, and it was limited to women (20). In the Singapore Chinese Health Study, Seow et al (20) reported an inverse association between isoflavone intake and total lung cancer among non-smoking women, with a multivariate-adjusted HR for lung cancer incidence in the highest compared with lowest quartile of isoflavone intake of 0.59 (95% CI: 0.38, 0.91), whereas no association was found in ever smokers.

Here, we observed a nonsignificant decrease in the risk of adenocarcinoma and total lung cancer in never-smoking women. It is possible that our data might not have sufficient statistical power to detect an association between isoflavone intake and lung cancer risk among never-smoking women. In addition, lack of information on passive smoking in never-smoking women at the time of exposure assessment may have masked a significant association, albeit that our additional analysis using information from the baseline survey on passive smoking did not materially change the results. Similar to our study, Seow et al’s (20) prospective study in nonsmoking women in Singapore reported a nonsignificant inverse association of isoflavone intake with risk of lung adenocarcinoma but a significant inverse association with other histologic types. In contrast, the only case-control study that showed results by histologic type, which was conducted among never-smoking women in Hong Kong, found an inverse association between tofu or soy and lung adenocarcinoma and large cell carcinoma (13). Thus, the results of these studies of risk in never smokers by histologic type were inconsistent.

In addition to its prospective study design, high response rate, and relatively low proportion of loss to follow-up, our study has several other strengths. Participants were recruited from the Japanese general population, which has relatively higher isoflavone intake than Western populations. Isoflavone intake was measured by a questionnaire with a reasonably high level of validity and reproducibility.

Several limitations of the study also warrant mention. First, behavior in adhering to isoflavone intake may have confounded the association between isoflavone intake and lung cancer risk. Previous studies in Japan reported that soy food intake was associated with other traditional or healthy food intakes (38–41). We therefore included intake of vegetables, fruit, and fish (18, 42), which may relate to lung cancer risk, into the multivariate model to investigate an independent association between isoflavone intake and lung cancer risk. Nevertheless, we cannot completely exclude the possibility that isoflavone intake is a marker of unmeasured factors. Second, we did not collect information on isoflavone supplement use. However, a relatively recent 2006 survey on supplement use in Japan showed a low prevalence of isoflavone supplementation (<1.6%) (43), and thus intake from supplements is considered to be negligible. Third, because we assessed isoflavone intake by using an FFQ, some misclassification of isoflavone intake may have arisen in estimating the effect on lung cancer risk. However, such misclassification was likely nondifferential and would tend to result in underestimation of the effect of isoflavone intake.

Although the mechanisms of this putative protective effect of isoflavones on lung carcinogenesis are not fully understood, not only estrogen-dependent (via the mediation of estrogen receptors) but also estrogen-independent mechanisms are possible. Genistein is a potent inhibitor of epidermal growth factor receptor (EGFR) kinase activity (44). In clinical findings, **EGFR** gene mutation in non–small cell lung cancer was a strong predictor of benefit from EGFR tyrosine kinase inhibitors (45). Taken together, these findings suggest that isoflavones may inhibit lung carcinogenesis through EGFR-mediated mechanisms. Because never-smoking status, East Asian ethnicity, and female sex are associated with **EGFR** gene mutation in lung cancers (45), we speculate that the EGFR-mediated mechanisms may be dominant and explain the present difference between smokers and...
never smokers in the association of isoflavone with lung cancer. In fact, a case-control study in Japan investigating the association between soy foods and non–small cell lung cancer by EGFR mutation status found an inverse association with EGFR-mutated lung cancer only (46). Further epidemiologic studies on the association of isoflavone intake with lung cancer risk by using information on EGFR mutation status would likely provide a better understanding of the mechanisms.

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REFERENCES


