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Authors
Kitahara, Cari M
Pfeiffer, Ruth M
Sosa, Julie A
et al.

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Impact of Overweight and Obesity on US Papillary Thyroid Cancer Incidence Trends (1995–2015)

Cari M. Kitahara, Ruth M. Pfeiffer, Julie A. Sosa, Meredith S. Shiels

Abstract

Background: Since the early 1980s, papillary thyroid cancer (PTC) incidence rates and the prevalence of obesity, a risk factor for PTC, have increased substantially in the United States. We estimated the proportion of PTC incidence in the United States attributable to overweight and obesity during 1995–2015.

Methods: National Institutes of Health-AARP Diet and Health Study cohort data (n = 457,331 participants, 50–71 years and cancer-free at baseline) were used to estimate multivariable-adjusted hazard ratios (HRs) for PTC across body mass index categories. Population attributable fractions (PAFs) were calculated using estimated hazard ratios and annual overweight and obesity prevalence estimates from the National Health Interview Survey. PAF estimates were combined with Surveillance, Epidemiology, and End Results-13 data to calculate annual percent changes in PTC incidence rates attributable (and unrelated) to overweight and obesity.

Results: Overweight (25.0–29.0 kg/m²) and obesity (≥30.0 kg/m²) were associated with 1.26-fold (95% confidence interval [CI] = 1.05- to 1.52-fold) and 1.30-fold (95% CI = 1.05- to 1.62-fold) increased risks of PTC, respectively, and nearly threefold (HR = 2.93, 95% CI = 1.25 to 6.87) and greater than fivefold (HR = 5.42, 95% CI = 2.24 to 13.1) increased risks of large (>4 cm) PTCs compared with normal weight (18.5–24.9 kg/m²). During 1995–2015, PAF estimates for overweight and obesity increased from 11.4% to 16.2% for all PTCs and from 51.4% to 63.2% for large PTCs. Overweight or obesity accounted for 13.6% and 57.8% of the annual percent changes in total (5.9%/y) and large (4.5%/y) PTC incidence rates, respectively, during 1995–2015.

Conclusions: Overweight and obesity may have contributed importantly to the rapid rise in PTC incidence during 1995–2015. By 2015, we estimate that one of every six PTCs diagnosed among adults 60 years or older, including nearly two-thirds of large PTCs, were attributable to overweight and obesity.
(all histologic types apart from medullary carcinoma) and, to a greater extent, thyroid cancer mortality (9–12). Based on the results from epidemiologic studies, the International Agency for Research on Cancer determined that there is sufficient evidence of a causal relationship between excess adiposity and thyroid cancer (13). Moreover, results from clinical studies have shown that obese PTC patients tend to present with more advanced-stage disease and clinically aggressive tumor characteristics (14–16), which may be attributable to a direct effect of excess adiposity on thyroid cancer growth and progression (17). Considering the tremendous increase in obesity prevalence among US adults since the early 1980s (from 15% in 1980 to nearly 40% in 2015–2016) (18,19), excess adiposity could have contributed appreciably to the observed temporal increases in US PTC incidence rates.

The overarching aim of the current study was to quantify the impact of the rising prevalence of overweight and obesity in the general US population on trends in PTC incidence rates (overall and by tumor characteristics at diagnosis) during 1995–2015. To estimate the risk of PTC associated with overweight and obesity, we analyzed data from a large US prospective cohort study and, for the first time in a cohort study to our knowledge, assessed this association according to tumor stage and size at diagnosis. We combined these results with national overweight and obesity prevalence and cancer registry data to estimate the proportions of PTCs diagnosed each year that were attributable to overweight and obesity.

Methods

Study Population and Case Definition

The National Institutes of Health-American Association of Retired Persons (NIH-AARP) is a large US cohort study that was established in 1995–1996 when 567,169 members of AARP (formerly known as the American Association of Retired Persons), aged 50–71 years, satisfactorily completed a mailed baseline questionnaire inquiring about health and lifestyle characteristics (20). For the analysis, we excluded proxy respondents, individuals who reported a prior diagnosis of cancer other than non-melanoma skin cancer, those with no follow-up information, individuals with missing data on smoking status, height, or weight; and cases with extreme values of BMI, yielding a total of 457,331 individuals (273,604 men and 183,727 women). Cancer diagnoses were obtained through 2011 by linking individual study participants with state and local cancer registry databases. Cases were diagnosed with first primary PTC during follow-up (ICD-10 C73.9; ICD-O-3 8050, 8260, 8340–8344, 8350, 8450–8460). Cases were further classified by stage at diagnosis (Surveillance, Epidemiology and End Results Program [SEER] summary stage: localized, regional, distant) and tumor size (<1.0, 1.1–2.0, 2.1–4.0, and >4.1 cm, corresponding to size thresholds used by the American Joint Committee on Cancer thyroid cancer staging system (21)). A secondary analysis was restricted to first primary anaplastic thyroid cancers (ICD-O-3 8020–8035). The study protocol was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Annual overweight and obesity prevalence data for adults aged 50 years or older during 1985–2005 were ascertained from the National Health Interview Survey (NHIS), a nationally representative survey of the health of the US civilian noninstitutionalized population (22). BMI was calculated from self-reported height and weight.

PTC incidence rates among those 60 years and older during 1995–2015 were estimated from data collected by 13 cancer registries as part of the SEER-13 (23). Cases were restricted to first primary thyroid cancers that were microscopically confirmed and classified using the histology codes and size categories described above.

Statistical Analysis

Using data from NIH-AARP, Cox proportional hazard regression models were used to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between BMI categories (<18.5 [underweight], 18.5–24.9 [normal weight], 25.0–29.9 [overweight], and ≥30.0 kg/m² [obese]) and first primary PTC risk. Follow-up started at participants’ age at baseline questionnaire completion and ended at the age at diagnosis of any primary cancer other than non-melanoma skin cancer or right-censoring (loss to follow-up, or death, or end of follow-up on December 31, 2011). Additional models estimated associations between BMI and PTC by tumor stage and size at diagnosis. Models were adjusted for sex, race or ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other specified and unknown), education (college graduate, not college graduate, unknown), weekly alcohol consumption (continuous), and smoking status (never, former, and current). The proportionality assumption was assessed by estimating the associations between BMI and PTC stratified by follow-up time. All P values were two-sided with an alpha of .05. Interaction tests were conducted by including a cross-product term in the model and evaluating the Wald-based P value.

National prevalence estimates of overweight (BMI = 25.0–29.9 kg/m²) and obesity (BMI ≥ 30.0 kg/m²) in the NHIS were calculated using sample survey weights. Because height and weight data were unavailable in 1986, 1989, and 1996, prevalence estimates for these years were imputed as the average of the surrounding years.

Annual population attributable fractions (PAFs) (24,25) were calculated from the estimated hazard ratios (relative risks) derived from the NIH-AARP Diet and Health Study and prevalence estimates from NHIS as

\[
P_{\text{AF}} = 1 - \frac{\sum_{i=1}^{n} w_i \exp(\gamma Z_i)}{\sum_{i=1}^{n} w_i \exp(\gamma Z_i + \beta X_i)}.
\]

In the above equation, \(w_i\) denotes the survey weight, \(Z_i\) the adjustment variables, \(X_i\) the variable of main interest (BMI category) for person \(i\) in the survey, and \(\gamma\) and \(\beta\) the log-relative risk parameters for \(Z\) and \(X\), respectively, estimated from the NIH-AARP cohort. Assuming a 10-year latency period based on a median time from questionnaire to PTC diagnosis in the NIH-AARP study of 8.9 years and available evidence regarding the latency period for other obesity–cancer associations (26), PAFs based on overweight and obesity prevalence estimates for a given year were applied to PTC incidence rates 10 years later. To accommodate the variability of the estimated log-relative risk parameters, we computed the variance of PAF both by a bootstrap resampling approach and analytically. Results are based on the bootstrap variance estimates, which agreed well with the analytic estimates. Estimated PAFs were then multiplied by annual age-standardized PTC rates for adults aged 60 years or older in SEER, partitioning out incidence rates attributable to (and unrelated
to) overweight and obesity. Annual percent changes in PTC rates and for overweight- and obesity-attributable and overweight- and obesity-unrelated PTC incidence rates were estimated using Joinpoint software, which identifies calendar years where there is a statistically significant change in the slope of incidence rate trends over time. Average annual percent changes (AAPCs) also were estimated for the full 1995–2015 time period. The proportion of the AAPC driven by overweight- and obesity-attributable PTC incidence rates was estimated as 1 – [AAPC_{overweight/obesity-unrelated} / AAPC_{overall}].

**Results**

From 1995 to 2011, 604 incident PTC cases occurred among men and women in the NIH-AARP Diet and Health Study (Table 1). Overweight (25.0–29.9 kg/m²) and obesity (≥30.0 kg/m²) were associated with 1.26-fold (95% CI = 1.05-fold to 1.52-fold) and 1.30-fold (95% CI = 1.05-fold to 1.62-fold) increased risks of PTC, respectively, compared with normal weight (18.5–24.9 kg/m²) (Table 2). Finer categorization of the top BMI categories showed consistently increasing risks of PTC with greater BMI, with hazard ratios for obese class I (30.0–34.9 kg/m²) of 1.21 (95% CI = 0.94 to 1.55), obese class II (35.0–39.9 kg/m²) of 1.40 (95% CI = 0.97 to 2.03), and obese class III (40+ kg/m²) of 1.93 (95% CI = 1.15 to 3.22) (Supplementary Figure 1, available online). Hazard ratios for continuous BMI were highest in the first 10 years of follow-up (0–4.9 years: HR = 1.08, 95% CI = 1.07 to 1.10; 5.0–9.9 years: HR = 1.05, 95% CI = 1.03 to 1.07; 10.0+ years: HR = 0.96, 95% CI = 0.95 to 0.98); the HR for continuous BMI over the full follow-up period was 1.03 (95% CI = 1.01 to 1.04). Associations were similar for localized versus regional and distant cases (Table 2). Overweight and obesity were associated with nearly threefold (HR = 2.93, 95% CI = 1.25 to 6.87) and greater than fivefold (HR = 5.42, 95% CI = 2.24 to 13.1) increased risks of large (>4 cm) PTCs compared with normal weight and were not associated with risk of smaller-sized PTCs. Hazard ratios by BMI category were similar for PTCs of less than 1 cm and those with missing or unknown size. Overall, BMI was more strongly associated with PTC risk in men than women (Supplementary Table 1, available online) (PInteraction [using continuous BMI] = .04). Among men, associations were stronger for regional and distant PTC compared with localized PTC. Statistically significant positive associations were observed for obesity in both sexes after restricting to PTCs greater than 4 cm at diagnosis (men: HR = 7.62, 95% CI = 2.11 to 27.5; women: HR = 3.58, 95% CI = 1.02 to 12.5; PInteraction = .36); no associations were observed for PTCs 4 cm or less in either men or women. No statistically significant interaction was observed between age at study entry (<60, 60+ years) and BMI (continuous) on PTC risk (PInteraction = .07). Overweight and obesity were associated with increased risk of anaplastic thyroid cancer (n = 28; HRs = 1.74, 95% CI = 0.63 to 4.77 and 3.59, 95% CI = 1.31 to 9.83, respectively) compared with normal weight.

The prevalence of obesity among NHIS survey respondents aged 50 years or older increased from 11.2% to 23.8% during 1985–2005, and the prevalence of overweight increased from 29.6% to 37.0% (Figure 1). In comparison, during the same calendar years, baseline (1995–1996) prevalence estimates of obesity and overweight among NIH-AARP participants were somewhat higher (21.4% and 43.0%, respectively; Table 1). Combining the NHIS prevalence estimates with the multivariable (including sex)-adjusted hazard ratios from the NIH-AARP study, we estimated that the PAF, or proportion attributable to overweight and obesity among US adults aged 50 years or older, increased from 11.4% (95% CI = 3.9% to 18.9%) to 16.2% (95% CI = 6.2% to 26.0%) during 1995–2015 (Figure 2). PAFs for the largest PTCs (>4 cm) increased from 51.4% (95% CI = 24.2% to 82.0%) to 63.2% (95% CI = 38.2% to 87.9%) during 1985–2005.

**Table 1.** Baseline characteristics and diagnostic information for individuals diagnosed with PTC during follow-up (cases) and non-cases in the NIH-AARP Study, 1995–2011

| Baseline or diagnostic characteristic | Cases No. (%) | Noncases No. (%) |
|--------------------------------------|--------------|-----------------|
| Total                                | 604 (100)    | 456 507 (100)   |
| Sex                                  |              |                 |
| Male                                 | 248 (41.1)   | 273 242 (59.9)  |
| Female                               | 356 (58.9)   | 183 265 (40.2)  |
| Age at baseline, y                   |              |                 |
| 50–54                                | 100 (16.6)   | 62 586 (13.7)   |
| 55–59                                | 167 (27.6)   | 104 002 (22.8)  |
| 60–64                                | 168 (27.8)   | 128 418 (28.1)  |
| 65–69                                | 155 (25.7)   | 145 482 (31.9)  |
| ≥70                                  | 14 (2.3)     | 16 019 (3.5)    |
| Education                            |              |                 |
| College graduate                     | 237 (39.2)   | 178 887 (39.2)  |
| Not college graduate                 | 340 (56.3)   | 265 499 (58.2)  |
| Unknown                              | 27 (4.5)     | 12 121 (2.7)    |
| Race/ethnicity                       |              |                 |
| Non-Hispanic white                   | 551 (91.2)   | 418 487 (91.7)  |
| Non-Hispanic black                   | 26 (4.3)     | 16 975 (3.7)    |
| Hispanic                             | 8 (1.3)      | 8504 (1.9)      |
| Other                                | 11 (1.8)     | 7423 (1.6)      |
| Unknown                              | 8 (1.3)      | 5118 (1.1)      |
| Smoking status                       |              |                 |
| Never                                | 268 (44.4)   | 166 984 (36.6)  |
| Former                               | 287 (47.5)   | 233 011 (51.0)  |
| Current                              | 49 (8.1)     | 56 512 (12.4)   |
| BMI, kg/m²                           |              |                 |
| <18.5                                | 1 (0.2)      | 3432 (0.8)      |
| 18.5–24.9                            | 196 (32.5)   | 158 930 (34.8)  |
| 25.0–29.9                            | 262 (43.4)   | 196 396 (43.0)  |
| 30.0–34.9                            | 96 (15.9)    | 72 169 (15.8)   |
| 35.0–39.9                            | 33 (5.5)     | 19 676 (4.3)    |
| ≥40.0                                | 16 (2.6)     | 5904 (1.3)      |
| Stage                                |              |                 |
| Localized                            | 432 (71.5)   | —               |
| Regional                             | 117 (19.4)   | —               |
| Distant                              | 36 (6.0)     | —               |
| Unknown                              | 19 (3.1)     | —               |
| Tumor size, cm                       |              |                 |
| ≤1.0                                 | 185 (30.6)   | —               |
| 1.1–2.0                              | 98 (16.2)    | —               |
| 2.1–4.0                              | 86 (14.2)    | —               |
| >4.0                                 | 50 (8.3)     | —               |
| Unknown                              | 185 (30.6)   | —               |

*Not applicable to noncases. BMI = body mass index; NIH-AARP = National Institutes of Health-American Association of Retired Persons; PTC = papillary thyroid cancer.
Table 2. Hazard ratios* and 95% confidence intervals for PTC, overall and by stage and tumor size, according to baseline categories of BMI in the NIH-AARP Diet and Health Study (1995–2011)

| Diagnostic characteristic | No. of cases | <18.5 | 18.5–24.9 | 25.0–29.9 | ≥30.0 |
|---------------------------|--------------|-------|------------|------------|-------|
| Total                     | 604          | 0.22  | (0.03 to 1.57) | 1.00 (Referent.) | 1.26 (1.05 to 1.52) | 1.30 (1.05 to 1.62) |
| Stage                     |              |       |            |            |       |       |
| Localized                 | 432          | 0.30  | (0.04 to 2.15) | 1.00 (Referent.) | 1.25 (1.00 to 1.56) | 1.28 (1.00 to 1.66) |
| Regional and distant      | 153          | —     | —          | 1.00 (Referent.) | 1.32 (0.90 to 1.93) | 1.39 (0.89 to 2.16) |
| Tumor size, cm            |              |       |            |            |       |       |
| ≤1                        | 185          | —     | —          | 1.00 (Referent.) | 1.28 (0.92 to 1.79) | 1.20 (0.81 to 1.78) |
| 1.1–2.0                   | 98           | —     | —          | 1.00 (Referent.) | 0.77 (0.48 to 1.23) | 1.09 (0.66 to 1.82) |
| 2.1–4.0                   | 86           | —     | —          | 1.00 (Referent.) | 1.42 (0.87 to 2.32) | 1.04 (0.56 to 1.92) |
| >4.0                      | 50           | —     | —          | 1.00 (Referent.) | 2.93 (1.25 to 6.87) | 5.42 (2.24 to 13.1) |
| Missing or unknown        | 185          | 0.74  | (0.10 to 5.35) | 1.00 (Referent.) | 1.30 (0.92 to 1.83) | 1.22 (0.82 to 1.82) |

*Models used attained age as the time metric and were adjusted for sex, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other specified, unknown), education (college graduate or not, unknown), number of drinks of alcohol per week (continuous), and cigarette smoking status (never, former, current). BMI = body mass index; CI = confidence interval; HR = hazard ratio; NIH-AARP = National Institutes of Health-American Association of Retired Persons; PTC = papillary thyroid cancer.

†No cases contributed to the category.

Discussion

Excess adiposity is an important risk factor for PTC (29), and both the prevalence of overweight and obesity and the incidence of PTC have increased substantially over the past four decades in the United States (1,19). Our study used an innovative approach that combined relative risk estimates with annual data from national health surveys and cancer registries to estimate the impact of overweight and obesity on US trends in PTC incidence rates, overall and stratified by stage and tumor size. Assuming a causal relationship, we estimated that one in six PTCs and two in three large PTCs diagnosed among US adults aged 60 years or older in 2015 may have been attributable to overweight and obesity. Furthermore, we estimated that in the absence of overweight and obesity, the increase in PTC incidence rates [particularly for the larger tumors, which require more aggressive clinical management (30)] would have been substantially lower.

Some have argued that the link between obesity and thyroid cancer may be at least partly explained by greater diagnostic scrutiny among patients with an underlying thyroid disorder (eg, hypothyroidism) or other obesity-related chronic conditions (31,32). For this to be the sole explanation for our findings, however, we would have expected overweight and obesity to be associated with an increased risk of small PTCs, which are more likely to be incidentally detected and indolent compared with larger PTCs. Instead, we found that the positive association between BMI and PTC risk was restricted to large (>4 cm) tumors. The lack of an association for small PTCs could reflect the greater challenges in detecting nodules of this size in obese patients through palpation or imaging (33,34). Greater delays in diagnosis among the obese participants (thus allowing for greater tumor growth) and/or more incidental detection of small PTCs among the normal-weight participants could also explain the patterns observed. On the other hand, a recent study found no difference in the method of initial detection of differentiated thyroid cancer (palpation, imaging, incidental) by obesity status (35). Without individual-level information on the pathways through which PTCs were detected and ultimately diagnosed in the NIH-AARP study, however, we could not fully evaluate or...
control for the effects of healthcare access and utilization on our results.

Our findings, particularly the strong associations between BMI and risks of larger-sized PTCs and anaplastic thyroid cancer, may also reflect a direct influence of excess adiposity on differentiated thyroid cancer growth and progression. Larger tumor size is associated with disease-specific survival and recurrence (36,37), and anaplastic thyroid cancers are highly lethal undifferentiated tumors that appear to evolve as part of the natural course of untreated differentiated thyroid cancer (38). Although the biological mechanisms underlying the relationship between adiposity and thyroid cancer are not fully understood, there have been tremendous advancements in knowledge regarding the complex mechanisms by which excess adiposity influences the induction and progression of cancer more generally (39–41). Many mechanisms, including hyperinsulinemia, chronic inflammation, and alterations in circulating adipokines (including leptin and adiponectin), appear to be shared across multiple cancer types, whereas others are site specific (39–41). Prolonged hyperinsulinemia promotes a favorable cellular environment for tumor progression, in part, through reduced production of insulin-like growth factor (IGF) binding protein-1 and -2 and elevated levels of free IGF-1. Insulin also directly influences tumor development through promotional and antiapoptotic effects. Among men and postmenopausal women, adipose tissue is the major source of estrogen exposure, and both obesity and circulating estrogen levels have been clearly linked to risks of postmenopausal breast and endometrial cancers (41). With regard to differentiated thyroid cancer specifically, recent epidemiologic and molecular studies support a possible mediating role of insulin and IGF-1, inflammatory, and leptin signaling pathways (17,42–48). Additional research is needed to better elucidate these and other plausible biological mechanisms underlying the obesity–thyroid cancer association, including estrogen- and thyroid hormone-mediated pathways.

A major limitation of our study was the reliance on self-reported height and weight data in both the NIH-AARP study and NHIS (49). Random and systematic errors in the reporting of weight and/or height may have contributed to the stronger hazard ratio estimates for men compared with women based on NIH-AARP study data. Previous studies suggested that women tend to underreport (and men overreport) their weight, and women and, to a greater extent, men tend to overreport height (50). Although random errors would have attenuated the hazard ratios, systematic errors could lead to either over- or underestimated hazard ratios (with estimates of PAF following in the same direction). NHIS data may have underestimated the prevalence of overweight and obesity prevalence in the United States, thus contributing to an underestimation of the PAFs (50). Unlike other national surveillance data, however, NHIS captured height and weight on an annual basis over the calendar period of interest, which enabled us to calculate annual estimates of PAF. The NIH-AARP study also offered several strengths, including the very large size, long length of follow-up, capture of detailed cancer diagnosis data (including histology, stage, and size), and individual-level information on several potential confounding factors. Nonetheless, if possible, our findings should be replicated in studies using measured height and weight data.

Our hazard ratio estimates directly assessed the relationship between overweight and obesity and PTC risk among middle-to-older-aged adults in the United States. Thus, our results may...
have limited generalizability to other populations. Similar analyses should be conducted using data from younger populations, because PTC risk may be more strongly associated with excess adiposity in adolescence and young adulthood (9,51), possibly reflecting greater susceptibility to the effects of metabolic and hormonal influences during periods of development and/or greater lifetime exposure to such effects (4).

Because PTCs are often slow-growing and there is a potentially large reservoir of undiagnosed indolent disease in the population, PTC incidence rates are highly sensitive to changes in clinical recommendations affecting detection and diagnosis, including those involving guidelines for the management and diagnostic work-up of thyroid nodules, thyroid cancer screening, medical surveillance and diagnostic imaging, and thyroid cancer coding and terminology (29,31,52–54). In the current study, we did not attempt to quantify the impact on PTC incidence trends of changes in medical practice, which appear to affect mostly small localized PTCs (29,31), or other environmental and lifestyle factors for PTC (4). Several clinical recommendations recently have been introduced or changed in response to concerns about thyroid cancer overdiagnosis and overtreatment (30,52), which may have contributed to the plateauing of PTC incidence rates since 2009 (1). In the future, PTC incidence rates may continue to remain stable or even decline because of these developments. If the prevalence of overweight and obesity continues to climb at a steady pace (19), the fraction of PTCs attributable to excess body weight also will increase, particularly if the impact of overdiagnosis on rising incidence rates subsides.

In summary, our results suggested that overweight and obesity may have contributed importantly to the rapid rise in PTC incidence during 1995–2015. By 2015, we estimated that one of every six PTCs diagnosed, including nearly two-thirds of large PTCs, among adults aged 60 years and older were attributable to overweight and obesity. Thus, a substantial number of PTCs, especially larger PTCs, could potentially be avoided by implementing public health interventions targeting overweight and obesity in the population.

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**Notes**

Affiliations of authors: Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics (CMK) and Biostatistics Branch, Division of Cancer Epidemiology and Genetics (RMP), National Cancer Institute, Rockville, MD; Department of Surgery, University of California San Francisco, San Francisco, CA (JAS); Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD (MSS).

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