Thyroid Cancer and Nonsteroidal Anti-Inflammatory Drug Use: A Pooled Analysis of Patients Older Than 40 Years of Age

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Background: Cyclooxygenase (COX-2) has been associated with tumor growth and metastasis in several cancers, including thyroid cancer. For this reason, several investigators have studied COX-2 inhibitors in preclinical models of thyroid cancer and found antineoplastic effects. Thus, the primary aim of this study was to assess if the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced incidence of thyroid cancer. A second aim of the study was to determine additional risk or protective factors for thyroid cancer.

Methods: Three large prospective population-based studies (the NIH-AARP Diet and Health Study; the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and the U.S. Radiologic Technologists Study) were pooled to investigate the association between self-reported frequency of aspirin and nonaspirin NSAID use one year prior to baseline (no use, ≤ 2 /week, >2 –6/week, and ≥ 7 /week) and subsequent risk of thyroid cancer. A Cox regression proportional hazard model was used to estimate aggregated hazard ratios (HR) adjusted for cohort, sex, race/ethnicity, weight, smoking status, and alcohol intake.

Results: There were 388,577 participants in the pooled cohort, with 481 cases of thyroid cancer. No significant risk reduction was observed with regular use of nonaspirin NSAIDs (HR = 1.14 [confidence interval (CI) 0.84–1.55]), and/or regular use of aspirin (HR = 1.06 [CI 0.82–1.39]). The multivariate regression analysis confirmed as previously reported in the literature that female sex, obesity class I (body mass index [BMI] = 30–34.99 kg/m²), and obesity class II (BMI = 35–35.99 kg/m²) were independently associated with an increased thyroid cancer risk. Current smoking status and moderate and excessive alcohol use were also confirmed as independent risk factors associated with a reduced thyroid cancer risk.

Conclusions: Neither nonaspirin NSAIDs nor aspirin use is associated with a reduced risk of thyroid cancer. Women and obesity are associated with an increased risk of thyroid cancer, whereas smoking and alcohol use are associated with decreased risk of thyroid cancer.

Introduction

THE INCIDENCE OF THYROID CANCER, the most common endocrine malignancy, has been increasing over the past three decades. Between 1995 and 2005, the incidence of thyroid cancer has increased by 98% in the United States (1). As the incidence of thyroid cancer rises, it is important to determine what preventive measures and risk-reduction approaches could be utilized to reduce thyroid cancer-related morbidity and mortality, as well as the cost of care (2).

Cyclooxygenase-2 (COX-2) has been closely associated with tumor growth and metastasis in a number of cancers such as lung, breast, colorectal, and cervical cancer (3,4).

Patients with chronic lymphocytic thyroiditis were three times more likely to have thyroid cancer, suggesting an association between chronic inflammation and cancer development (5,6). Overexpression of COX-2 has been observed in thyroid follicular cells of patients with Hashimoto's thyroiditis but not in normal thyroid or multinodular goiter tissue (7,8). Several studies have demonstrated an overexpression of COX-2 in papillary thyroid cancer (PTC) compared with normal thyroid and multinodular goiter tissue (7,9,10).

In addition, the expression of COX-2 is associated with older age, lymph node metastasis, and advanced stage in patients with thyroid cancer (11,12). *In vitro* studies of thyroid cancer cell lines have shown that a selective inhibitor of

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COX-2, NS-398, can inhibit proliferation (13), and reduce cellular migration and invasion (14). In esophageal cancer, COX-2 expression has also been shown to be associated with anti-apoptosis (15). These findings suggest a role of COX-2 in thyroid cancer development, and the potential of COX-2 as a chemopreventive and therapeutic target. This approach has been studied most notably in colorectal cancer. Chan *et al.* analyzed a large prospective cohort study of 82,911 women enrolled in the Nurses' Health Study and reported a multivariate relative risk (RR) of 0.77 [confidence interval (CI) 0.67–0.88] among women with regular long-term aspirin use. The use of aspirin and the multivariate RR was also found to be dose dependent, and a similar trend was seen for NSAIDs as well (16). Given the findings of *in vitro* studies and the promising results of this study in colorectal cancer, aspirin and NSAID use may reduce thyroid cancer incidence.

While the evidence strongly supports the chemopreventive effect of NSAIDs in colorectal cancer (17), there is no population-based study that addresses whether NSAIDs may reduce the risk of thyroid cancer. It was hypothesized that the incidence of thyroid cancer would be lower in individuals taking NSAIDs. Therefore, the primary objective of this study was to evaluate whether NSAID use reduces the risk of thyroid cancer in a large prospective population-based cohort.

Materials and Methods

Data sources

The data source consisted of three National Cancer Institute (NCI) cohorts: (i) the National Institutes of Health-the American Association of Retired Persons Diet and Health Study (NIH-AARP); (ii) the Prostate, Lung, Colorectal and Ovarian (PLCO); and (iii) the U.S. Radiologic Technologist (USRT) Study. Each cohort met the following criterion: individual assessment of aspirin and nonaspirin NSAID use within a similar time frame. Each cohort had individual questions for the use of aspirin and nonaspirin NSAID use. The three studies all had Institution Review Board approval at the National Institutes of Health.

NIH-AARP Study. NIH-AARP, initiated in 1995–1996, is a prospective cohort study examining the diet and lifestyle factors of AARP members aged 50–71 years in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A self-administered baseline questionnaire was mailed to 3.5 million members of AARP aged 50–71 years in 1995–1996 and was returned by 617,119 individuals (17.6%) (18). In 1996–1997, a second questionnaire containing information on NSAID use was completed by 334,908 participants. The study follow-up period was from 1996 to 2003.

PLCO Cancer Screening Trial. PLCO, a multicenter trial, evaluated the effectiveness of prostate, lung, colorectal, and ovarian cancer screening with respect to disease-specific mortality (19,20). Between October 1993 and July 2001, 154,952 subjects (49.5% men) aged 55–74 years were enrolled at 10 U.S. screening centers (Washington, DC; Detroit, Michigan; Salt Lake City, Utah; Denver, Colorado; Honolulu, Hawaii; Minneapolis, Minnesota; Marshfield, Wisconsin; Pittsburgh, Pennsylvania; St. Louis, Missouri; and Birmingham, Alabama).

At the initial screening, a questionnaire (completed by 96.8% of participants) was administered that included items about NSAID use. The study follow-up period was from 1993 to 2005.

USRT Study. USRT, a prospective cohort study, was designed to evaluate the health history of radiologic technologists who had been certified for at least two years by the American Registry of Radiologic Technologists between 1926 and 1980 (21,22). From 1994 to 1998, a questionnaire was sent to all living individuals (126,628 participants), which ascertained NSAID use. The questionnaire was returned by 90,972 participants (71.8%). The study follow-up period was from 1994 to 2004.

Thyroid cancer case ascertainment

The pooled population consisted of 388,577 individuals, with 481 individuals (163 male) with thyroid cancer, as ascertained by follow-up questionnaires for NIH-AARP, PLCO, and USRT. Screening protocols for thyroid cancer were not instituted in any of the three pooled protocols.

Assessment of NSAID use and aspirin use

The frequency of NSAID and aspirin use was ascertained by analyzing data from self-administered questionnaires. NIH-AARP and USRT questionnaires investigated aspirin and general nonaspirin NSAID use (USRT: Ibuprofen, Motrin, Naprosyn, Advil; NIH-AARP: generic ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, Fenoprofen). PLCO investigated specifically aspirin- and ibuprofen-containing products (Advil, Nuprin, Motrin, etc.). Participants were advised to not include Tylenol or other pain relievers in their reports. Four categories for frequency of NSAID and aspirin use within the past 12 months were created based on previous literature and analysis (23): no use (referent), no regular use (≤ 2 times/week), regular use less than daily (> 2 –6 times/week), and regular daily use (≥ 7 times/week). The total duration of NSAID or aspirin use was not captured in any cohort. Nonaspirin NSAID and aspirin use were both included as independent variables in the multivariate analysis.

Covariate information

All of the studies collected information regarding sex, race/ethnicity, weight and height, smoking status, and alcohol status. In order to assess whether the cohorts were comparable and appropriate to be pooled, a hazard ratio (HR) of heterogeneity between studies was calculated. The HRs of heterogeneity between studies were assessed using the I^2 index and the Mantel–Haenszel test for heterogeneity (24,25).

Statistical methods

A Cox proportional hazard model was used to calculate study-specific hazard ratios and confidence intervals for the association of aspirin and NSAID use with thyroid cancer risk with age as a time metric. Follow-up started at age at baseline, which was defined as the time when NSAID exposure was recorded. The follow-up ended at age at thyroid cancer

diagnosis or age at censoring, which included diagnosis of any other cancer, death, or the end of the study.

The three cohorts were aggregated into one pooled cohort. Cohort-specific confounding variables were included in the final model. The NIH-AARP cohort assessed smoking status and smoking intensity by measuring cigarettes per day (never use, former use of 1–20, former use of 21–40, former use of ≥41, current use of 1–20, current use of 21–40, current use of ≥41), race/ethnicity (white, other), body mass index (BMI; 18.2 ≤ 25 kg/m², 25 ≤ 30 kg/m², and ≥30 kg/m²), alcohol use (g), and sex. The PLCO and USRT cohort assessed smoking status (nonsmoker, former, current), race/ethnicity (white, other), BMI, alcohol use (g), and sex.

Confounding variables were homogenized between the studies by creating common variables: smoking (nonsmoker, former, current), race/ethnicity (white, other), BMI (<25 kg/m², 25–29.99 kg/m², 30–34.99 kg/m², and >35 kg/m²), and alcohol status (nondrinker, moderate <14 g, heavy >14 g). Additional analyses assessing thyroid pathology by histologic subtype were not completed given that the number of patients with thyroid cancer incidence was low. Analyses were stratified by sex, smoking status, alcohol status, and BMI.

Results

There were 388,577 individuals (200,601 male) in the pooled cohort, with 481 cases of all subtypes of thyroid cancer (163 male). A total of 4,302,158.84 person-years were accrued in the cohort analyzed. Characteristics of thyroid cancer incidence, NSAID use, and aspirin use are summarized in Table 1. Selected demographic characteristics of the cohort are summarized in Table 2. Heterogeneity of the data due to cohort variability was assessed and shown to be similar (Fig. 1).

No significant risk reduction in thyroid cancer incidence was observed with nonaspirin NSAIDs and/or aspirin use (Table 3). The independent factors (Table 4) associated with increased thyroid cancer risk confirmed by a multivariate

analysis included female sex (HR 1.71 [CI 1.40–2.10], $p < 0.001$), obesity class I (BMI 30–34.99 kg/m²; HR 1.41 [CI 1.08–1.84], $p = 0.010$), and obesity class II (BMI 35–35.99 kg/m²; HR 1.69 [CI 1.21–2.36], $p = 0.002$). As previously documented in the literature, current smoking status and moderate and excessive alcohol use was associated with a reduced risk compared to nondrinkers (HR 0.65 [CI 0.46–0.92], $p = 0.015$; HR 0.78 [CI 0.63–0.97], $p = 0.024$; HR 0.68 [CI 0.50–0.93], respectively). USRT cohort affiliation was associated with an increased risk of thyroid cancer (HR 2.21 [CI 1.78–2.75], $p < 0.001$).

Subanalysis of risk factors did not show any lower risk of thyroid cancer with the consumption of either aspirin or NSAID. Given the relatively low incidence of thyroid cancer, a subtype analysis was not sufficiently powered and not evaluated. Data on the type of thyroid cancer and extent of disease were also not available.

Discussion

The current study is the largest prospective multicohort analysis evaluating the role of NSAID use and risk of thyroid cancer. This study shows that the use of nonaspirin NSAID or aspirin was not associated with a reduced incidence of thyroid cancer. The pooled analysis confirms the protective association of thyroid cancer incidence and smoking and alcohol use, and the higher risk of thyroid cancer associated with obesity and female sex.

Tissue analysis of thyroid cancer has shown that COX-2 expression is upregulated in patients with thyroid cancer compared with adjacent normal thyroid tissue (10), and these findings were validated with immunohistochemistry findings showing COX-2 expression to be higher in patients with PTC (26). Furthermore, chronic inflammation with increased expression of COX-2 has been associated with cancer (27) and PTC (5,6). Thus, it was postulated that NSAID use could potentially reduce inflammation and reduce the risk of cancer, as demonstrated in colorectal cancer (16,28). Therefore,

TABLE 1. CHARACTERISTICS OF THE COHORT STUDIES INCLUDED IN THE MULTICOHORT ANALYSIS OF ASPIRIN AND NONASPIRIN NSAID USE AND RISK OF THYROID CANCER AMONG MEN AND WOMEN, NIH-AARP, PLCO, USRT

Study	Follow-up period	No. of subjects in the baseline cohorts	No. of thyroid cases	Baseline median age, years (IQR)	Prevalence of aspirin use, %				Prevalence of nonaspirin NSAID use, %			
					No use	≤2/ week	>2–6/ week	≥7/ week	No use	≤2/ week	>2–6/ week	≥7/ week
Overall	1993–2005	388,577	481	61.3 (55.7–66.0)	33.8	30.4	13.4	22.4	45.7	33.8	10.9	9.6
Men		200,764	163	62.4 (57.4–66.7)	26.0	29.5	15.3	29.2	50.2	31.9	10.3	7.7
Women		187,813	318	60.0 (53.5–65.4)	42.1	31.3	11.4	15.2	41.0	35.8	11.5	11.7
NIH-AARP	1996–2003	269,553	292	62.8 (58.0–66.7)	26.5	31.6	16.9	25.0	43.3	33.2	13.4	10.0
Men		157,880	130	63.1 (58.2–66.8)	21.2	31.0	17.5	30.3	46.0	34.1	12.0	7.9
Women		111,673	162	62.5 (57.7–66.5)	34.0	32.4	16.1	17.5	39.5	32.0	15.3	13.1
PLCO	1993–2005	58,433	56	62.0 (58.0–67.0)	51.2	13.8	8.5	26.5	70.9	13.7	5.6	9.7
Men		29,314	16	62.0 (58.0–67.0)	46.1	14.0	9.1	30.8	75.4	12.5	4.5	7.5
Women		29,119	40	62.0 (58.0–67.0)	56.3	13.6	7.8	22.3	66.4	15.0	6.7	11.9
USRT	1994–2004	60,591	133	45.5 (41.4–51.7)	49.4	41.0	2.6	7.0	32.1	55.4	5.0	7.4
Men		13,570	17	47.6 (43.2–54.6)	38.7	46.0	3.1	12.2	43.9	47.5	3.1	5.5
Women		47,021	116	44.8 (40.5–51.3)	52.6	39.5	2.4	5.5	28.8	57.7	5.5	8.0

NSAIDs, nonsteroidal anti-inflammatory drugs; NIH-AARP, the National Institutes of Health-the American Association of Retired Persons Diet and Health Study; PLCO, the Prostate, Lung, Colorectal and Ovarian; USRT, the U.S. Radiologic Technologist.

TABLE 2. SELECTED CHARACTERISTICS OF PARTICIPANTS BY ASPIRIN AND NONASPIRIN NSAID USE IN A POOLED ANALYSIS, NIH-AARP, PLCO, USRT

	Aspirin						Nonaspirin NSAID					
	No use		≤2/week		>2–6/week		≤2/week		>2–6/week		≥7/week	
	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%
Baseline age, years	60.3 (54.4–65.7)		59.8 (53.9–65.1)		62.1 (57.3–66.3)		63.7 (59.0–67.3)		60.8 (55.9–65.5)		62.0 (56.8–66.5)	
Sex: Female		42.1		31.3		11.4		15.2		35.8		11.7
Race: white		33.8		30.4		13.4		22.4		33.8		9.6
BMI, kg/m ²	25.8 (23.2–29.2)		25.8 (23.3–28.8)		26.1 (23.7–29.1)		26.6 (24.3–29.7)		25.8 (23.3–28.9)		27.4 (24.3–31.0)	
Smoking status												
Never		37.7		31.3		12.7		18.3		34.6		9.0
Former		30.2		29.4		14.1		26.4		33.2		10.1
Current		34.4		31.2		13.3		21.0		33.1		9.6
Alcohol status												
Nondrinker		37.7		28.3		11.8		22.2		32.0		11.0
Moderate		34.8		31.2		13.0		21.0		34.8		9.4
Excessive		27.2		29.9		16.2		26.7		32.4		8.9

BMI, body mass index.

FIG. 1. Forest plot of hazard ratios separated by cohorts for both nonaspirin nonsteroidal anti-inflammatory drugs and aspirin use. P-heterogeneity scores calculated to assess for cohort heterogeneity.

NSAID use could potentially reduce the risk of thyroid cancer, which has financial and health-related consequences. However, the present analysis did not reveal a reduced risk of thyroid cancer with NSAID use in a population-based cohort study. This may be due to many factors including an older median age of the cohort, short duration of known NSAID use, an insufficiently large enough study cohort given the low incidence of thyroid cancer in these three pooled cohorts, and relatively short duration of follow-up period. In the Nurses' Health Study, Chan *et al.* did not see a relative risk reduction of colorectal cancer incidence until patients were ingesting aspirin or NSAIDs for at least a decade (16). The lack of screening and the indolent natural history of thyroid cancer may have confounded the results.

The increasing incidence of thyroid cancer has been associated with the detection of occult disease by numerous authors. Udelsman *et al.* showed that the incidence rates were significantly correlated with the density of endocrinologists and the employment of cervical ultrasonography (29). Access

to care is associated with the incidence of PTC, as documented by Morris *et al.* in an analysis of the Surveillance, Epidemiology, and End Results (SEER) database. In that study, thyroid cancer incidence was significantly higher in those over older than 65 years of age (annual percentage change 8.8%) compared with those younger than 65 (annual percentage change 6.4%) who do not have universal health-care (30). Increasing access to healthcare may explain the negative association with obesity. Obesity may be a surrogate for increased use of healthcare resulting in an increased incidence of thyroid cancer due to increased imaging use. Morbidly obese patients have an 81% greater per capita healthcare expenditure compared with normal-weight adults. Among the reasons for increased expenditures, morbidly obese adults had increased office-based visits and outpatient hospital care (31). Likewise, smoking and alcohol may be associated with a lowered incidence by a lower healthcare access or use by that subset of patients. The lack of association between NSAID use and thyroid cancer incidence

TABLE 3. THYROID CANCER RISK AND USE OF NONASPIRIN NSAIDS OR ASPIRIN AMONG MEN AND WOMEN IN A POOLED ANALYSIS, NIH-AARP, PLCO, USRT

	Overall			Male			Female		
	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Nonaspirin NSAIDs									
No use	190	1.00	Ref	76	1.00	Ref	114	1.00	Ref
Nonregular	184	1.11	[0.89–1.37]	58	1.11	[0.78–1.59]	126	1.11	[0.85–1.45]
>2–6/week	54	1.10	[0.81–1.50]	17	1.02	[0.59–1.74]	37	1.16	[0.80–1.70]
≥7/week	53	1.14	[0.84–1.55]	12	0.91	[0.49–1.86]	41	1.26	[0.88–1.81]
Aspirin									
No use	175	1.00	Ref	38	1.00	Ref	137	1.00	Ref
Nonregular	152	1.03	[0.83–1.29]	47	1.04	[0.67–1.60]	105	1.05	[0.81–1.36]
>2–6/week	64	1.20	[0.89–1.61]	25	1.12	[0.67–1.88]	39	1.28	[0.88–1.84]
≥7/week	90	1.06	[0.82–1.39]	53	1.25	[0.82–1.92]	37	0.88	[0.61–1.28]

HR, hazard ratio; CI, confidence interval.

TABLE 4. THYROID CANCER RISK SELECTED FACTORS AMONG MEN AND WOMEN IN A POOLED ANALYSIS, NIH-AARP, PLCO, USRT

	<i>Overall</i>		<i>Male</i>		<i>Female</i>	
	<i>HR</i>	<i>CI</i>	<i>HR</i>	<i>CI</i>	<i>HR</i>	<i>CI</i>
Smoking status						
Nonsmoker	1.00	Ref	1.00	Ref	1.00	Ref
Former	0.90	[0.74–1.09]	1.09	[0.77–1.54]	0.81	[0.64–1.04]
Current	0.65	[0.46–0.92]	1.11	[0.62–1.98]	0.51	[0.33–0.79]
Alcohol status						
Nondrinker	1.00	Ref	1.00	Ref	1.00	Ref
Moderate	0.78	[0.63–0.97]	0.88	[0.59–1.31]	0.72	[0.56–0.93]
Heavy	0.68	[0.50–0.93]	0.71	[0.45–1.14]	0.65	[0.42–1.01]
Obesity (BMI, kg/m ²)						
<25	1.00	Ref	1.00	Ref	1.00	Ref
25–29.99	1.12	[0.91–1.39]	1.30	[0.88–1.91]	1.06	[0.82–1.38]
30–34.99	1.41	[1.08–1.84]	1.44	[0.88–2.34]	1.44	[1.05–1.98]
>35	1.69	[1.21–2.36]	3.41	[1.94–5.97]	1.25	[0.82–1.91]

Bold indicates $p < 0.05$.

might be explained by the presence of these confounding factors. Nevertheless, the protective effects of smoking and alcohol have to be weighed against the well-documented known associated diseases, especially given the low morbidity of thyroid cancer and excellent prognosis for early stage disease.

Radiation exposure may be a confounding variable, since the USRT cohort was included in this pooled analysis. However, an analysis of these patients with occupational radiation exposure has shown that total duration of occupation, employment below the age of 20, and years performing diagnostic, therapeutic, and nuclear medicine procedures was not associated with thyroid cancer incidence (32). The USRT cohort has also been compared to age-specific, sex-specific, and race-specific matched individuals in the SEER program. The incidence of thyroid cancer is increased, but has been attributed to this population having increased access to imaging studies. An analysis showed that the frequency of thyroid tumors ≤ 1 cm was twice as high in the USRT cohort (30% vs. 15%) compared with data obtained from the SEER tumor registries. Furthermore, larger thyroid tumors (1.5–2.5 cm) were found in 19% of participants in the USRT cohort compared with 28% of registrants in the SEER database (21). Therefore, occupational radiation exposure in the USRT cohort was unlikely to have compromised the pooled analysis results.

In summary, the use of NSAIDs was not associated with a reduced risk of thyroid cancer. The data analysis confirms, as previously reported in the literature, that obese patients have a higher risk of thyroid cancer, and that current smoking and moderate alcohol use are associated with a lower risk of thyroid cancer. Therefore, contrary to the chemopreventive effects of NSAIDs in colorectal cancer, the present analysis does not support the use of NSAIDs to reduce the risk of thyroid cancer.

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Author Disclosure Statement

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