Long-term Risk of Thyroid Cancer After Initially Negative Thyroid Biopsy Results

Thyroid nodules are common, occurring in more than 50% of the general population. Historically, thyroid nodules characterized as benign were followed up indefinitely, often with multiple subsequent biopsies based on growth. Current evidence derived from sampled populations suggests that the rate of malignant neoplasms among benign thyroid nodules after long-term follow-up is low. We used data from an entire population to define the risk of being diagnosed with thyroid cancer in long-term follow-up of individuals with benign thyroid biopsy results.

Methods | A cross-sectional analysis of population-based data from a comprehensive administrative health database in Ontario, Canada, was performed. All thyroid biopsies in the province performed from January 1, 1991, to December 31, 2010, were identified from the provincial single payer physician-billing plan and linked to the Ontario Cancer Registry until December 31, 2014, to detect all cases of differentiated thyroid cancer with a follow-up of up to 24 years. Thyroid cancers diagnosed previously or within 1 year after first biopsy were excluded from analyses. This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Canada. Patient consent was waived by this board because health care databases were anonymously linked using encrypted identifiers to safeguard confidentiality. Investigators had no direct access to the study population.

Results | During the study period, 146,014 individuals underwent at least 1 thyroid biopsy. Results of 135,676 biopsies (92.9%) were initially benign. Of the patients with a benign nodule, the mean (SD) age at biopsy was 52.2 (13.4) years, 81.2% were females, and 18.8% were males.

During the study period, the number of biopsies performed in the province that were initially benign increased from 2280 per year in 1991 (22.1 per 100,000 inhabitants) to 12,074 per year in 2010 (91.5 per 100,000 inhabitants), as shown in Figure 1. In follow-up of patients with benign nodules, 6,354 had a diagnosis of thyroid malignant neoplasm during the follow-up period (396 per 100,000 person-years). The cumulative risk of being diagnosed with thyroid cancer within the follow-up period was 4.6% after 10 years and 7.5% after 24 years (Figure 2).

Discussion | In this population-based, longitudinal study, the cumulative risk of developing thyroid cancer among patients with initially negative thyroid biopsy results who were followed long-term was 7.5% after 24 years. Consistent with the literature, performance of thyroid biopsies increased 4.1-fold between 1991 and 2010. The risk of a malignant neoplasm after benign results of an index biopsy in our population was higher compared with the recent literature showing rates between 0.3% and 2.4% after less than 10 years of follow-up. There are some differences that may explain the rates seen in this large population. First, the definition of benign cytology in Ontario has, until adoption of the Bethesda classification, been variable. Because this cohort spans 24 years and begins in 1991, there were at least 17 years of patient data for which cytologic findings were not standardized. Further insight into the cancer rate we found within the population could be associated with the substantially longer follow-up period and therefore may include delayed malignant transformation of nodules not captured in shorter follow-up studies.

Figure 1. Population-Standardized Annual Number of Initial Benign Biopsy Results and the Risk of Subsequently Developing Cancer

![Graph showing population-standardized annual number of initial benign biopsy results and the risk of subsequently developing cancer.](https://jamanetwork.com/)
The study design strengthens the validity of these results. The administrative health databases from Ontario are more than 95% complete for cancer diagnosis and procedures. By capturing an entire population, our study was less susceptible to the types of selection biases and confounding that may have influenced other studies.

Limitations to this study include the lack of patient-specific clinical information such as results of ultrasonography and pathologic tests. In addition, changes in specimen management and diagnostic criteria over time may have influenced the rate of carcinoma because of more incidentally found microcarcinomas. Although the rate of carcinoma may have increased, these diagnoses are likely predominantly due to a clinically irrelevant entity.

Based on a large provincial population followed long-term after initially benign results of thyroid biopsy, the rate of malignant neoplasms was low, which questions the need of follow-up biopsies for all patients. Because cumulative risk of thyroid cancer in these patients is higher than the baseline lifetime risk of the population, further large risk stratification studies incorporating standard ultrasound biopsy data are needed to identify those requiring long-term follow-up.

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Use of Clinical Trial Registries in Otolaryngology Systematic Reviews

Systematic reviews are foundational to evidence-based patient care, yet these reviews are criticized for including only statistically significant findings to estimate summary effects, which may lead to publication bias. The exclusion of nonsignificant and/or unpublished results can lead to an overrepresentation of an intervention’s actual effect and potentially imprecise clinical decision making. Although many methods exist to minimize publication bias in systematic reviews, the use of clinical trial registries (CTRs) is particularly encouraging.

Clinical trial registries index new and ongoing studies, and may provide access to ongoing trial data prior to a study’s print release, even if nonsignificant findings arise.