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Examining the accuracy of self-reported smoking-related exposure among recently diagnosed non-muscle invasive bladder cancer patients

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Abstract

Purpose: Cigarette smoking is a risk factor for developing non-muscle invasive bladder cancer (NMIBC) and continued smoking exposure after diagnosis may increase the likelihood of adverse clinical outcomes. Here we compare self-reported vs. biochemically-verified nicotine exposure to determine the accuracy of self-report among recently diagnosed NMIBC patients.

Materials & Methods: This cross-sectional analysis consisted of 517 NMIBC patients who contributed a urine or saliva specimen the same day as self-reporting their smoking, use of e-cigarettes, nicotine replacement therapy (NRT), and whether they lived with a smoker. Cotinine, the primary metabolite of nicotine, was used as an objective biomarker of recent nicotine exposure.

Results: The prevalence of high, low, and no cotinine exposure was 13%, 54% and 33% respectively. Overall, 7.3% (38/517) of patients reported being a current cigarette smoker while 13% (65/517) had cotinine levels consistent with active smoking exposure. Of these 65 patients, 27 denied current smoking, resulting in a sensitivity of self-reported current smoking of 58%.

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After considering other sources of nicotine exposure such as e-cigarettes, cigars, NRT, and living with a smoker, the sensitivity was higher, at 82%. Nearly all patients with low cotinine denied any smoking-related exposure.

Conclusions: Our findings suggest either biochemical verification with cotinine or additional questions about other sources of nicotine are needed to accurately identify NMIBC patients who have smoking-related exposures. Accurate classification of active and passive smoking exposure is essential to allow clinicians to advise cessation and help researchers estimate the association between post-diagnosis smoking-related exposure and NMIBC recurrence risk.

Brief Description:

NMIBC self-report vs biochemical verification of smoking

Keywords

Bladder Cancer; Smoking; Cotinine

Introduction

Cigarette smoking is an established risk factor for developing non-muscle invasive bladder cancer (NMIBC). While some studies show persistent smoking after diagnosis is related to bladder tumor recurrence risk[1–3], other studies have found no such association[4,5]. The inconsistent associations from prior studies may in part be attributable to their reliance on self-reported smoking status. Cotinine is the primary metabolite of nicotine and is an established, reliable biomarker of recent smoking-related exposure[6]. Prior studies comparing misclassification rates between self-reported current cigarette smoking status and biochemically-verified cotinine levels in general population smokers, suggest up to 32% of active smokers misreport their smoking status[7]. We and others have found similarly high misreporting rates among cancer patients ranging from 27% in breast to 55.6% in lung[8–10]. The high misclassification rates based on self-report may be explained by patients not wanting to disclose they are currently smoking as well as the possibility of non-smokers being exposed to nicotine from other sources.

Accurately capturing a patient's smoking status is especially challenging today given the changing landscape of tobacco-related product use in this country. Current cigarette smoking and secondhand smoking exposure prevalence has declined over time[11], while cigar and smokeless tobacco use has remained stable[12]. Nondaily light smoking has also increased. Electronic cigarette use is rapidly increasing[13]. Moreover, polytobacco use (defined as using at least two tobacco-related products) is also becoming more common, even among cancer patients[14–17]. Biochemical verification may be necessary to accurately classify smoking-related exposures among cancer patients in research studies. In this report, we quantitatively assessed the relationships between self-reported cigarette smoking status and cotinine levels while considering other sources of nicotine exposure in a large cohort of recently diagnosed NMIBC patients.

Materials and Methods

Study Cohort.

The Determinants of Bladder Cancer Recurrence Study (The DETER Study) study is an American Cancer Society-funded, prospective cohort study approved by the Memorial Sloan Kettering Cancer Center (MSK) Institutional Review Board. The main objective of this study is to determine how biochemically-verified nicotine is associated with risk of recurrence among NMIBC patients undergoing treatment and surveillance at MSK. Eligible subjects were 18 years and older, had histologically-confirmed non-muscle invasive bladder cancer (<T2) within 36 months of consent, had an intact bladder, were English speaking and did not have any condition, in the opinion of the MSK clinician, that precluded their ability to provide consent or comply with study procedures. Of the 667 eligible patients undergoing surveillance and treatment at MSK between March 2015 and May 2018, 547 (82%) consented to the study. At the time of enrollment, patients agreed to complete questionnaires that captured self-reported cigarette smoking, tobacco use and other sources of nicotine exposure and contribute a biospecimen to be tested for cotinine. The consent explicitly stated the purpose of the biospecimen was to test for recent cigarette smoking and nicotine exposure. The present cross-sectional analysis was restricted to patients whose biospecimen was collected on the same day as their questionnaire (n=517, 95%).

Self-reported smoking and other sources of nicotine exposure.

Trained interviewers administered in-person questionnaires during clinic visits. Using standard items for assessing cigarette smoking[18], patients were considered ever cigarette smokers if they reported smoking 100 cigarettes in their lifetime. Ever cigarette smokers were asked about their current cigarette smoking behavior (i.e. every day, some days, not at all) and the age they started smoking cigarettes regularly. Current and former cigarette smokers were also asked how often they currently use nicotine replacement therapy (NRT) or use electronic cigarettes (every day, some days or not at all). Former smokers reported the age they stopped smoking. To assess secondhand smoke (SHS) exposure, all patients were asked whether they currently live with a smoker (yes/no). Participants could tell the interviewer about their use of other forms of tobacco use (e.g., pipes, cigars or smokeless tobacco) but this information was not collected systematically. In sum, smoking-related exposures included cigarettes, electronic cigarettes, cigars, NRT and living with a smoker. Clinical data, including pathologic stage (pTa, pT1, pTis) and grade (low, high) were abstracted from electronic medical records.

Biochemically-verified nicotine exposure.

Participants could contribute a urine and/or saliva specimen for biochemical verification of recent nicotine exposure. Cotinine was assessed biochemically using an enzyme-linked immunosorbent (ELISA) assay with the commercial High Sensitivity Salivary Cotinine Quantitative kit (Salimetrics) following manufacturer's recommendations and well-established QA and QC procedures (see Supplemental Material for details). Previously published cut-points were used to classify participants into high, low and no cotinine exposure for each specimen type. For urinary cotinine, the cut-points were ≥31.5 ng/mL for high exposure, ≥1.0–<31.5 ng/mL for low exposure, and <1.0 ng/mL no exposure[19].

For salivary cotinine, the cut-points were ≥3 ng/mL for high exposure, ≥1.0–<3 ng/mL for low exposure, and <1.0 ng/mL for no exposure[6]. To justify analyzing both specimen types together, we compared biochemical classification in 16 paired samples and found 100% concordance in patients classified as active vs low/no cotinine. The cotinine assay precision and other quality parameters are described in the Supplemental Material.

Statistical Approach.

Frequencies and percentages were used to describe prevalence of self-reported smoking-related exposures and of cotinine levels. We first calculated sensitivity and specificity from a 2×2 table that compared biochemically-verified cotinine levels (high exposure vs. low/no exposure) against self-reported current smoking (yes vs. no). Next, we calculated sensitivity after considering other sources of nicotine exposure. Finally, we report how different sources of smoking-related exposures were related to different cotinine levels (high/low/no cotinine exposure). All statistical analyses were performed using R version 3.5.2 (R Core Team).

Results

Table 1 presents demographic and clinical characteristics of the 517 DETER study participants who provided a urine or saliva sample on the same day as self-reporting their smoking-related exposures. The study cohort was predominantly white (89%), male (79%) and had a college education or above (64%). Median age at interview was 69 years. Most tumors were high grade (70%) and pTa stage (59%). Most patients provided a urine (93%) as opposed to saliva (7%) specimen for cotinine testing.

The prevalence of self-reported current, former and never smoking was 7%, 57% and 36%, respectively. Of the 38 self-reported current smokers, 8 reported concurrently using NRT (21%), 4 electronic cigarettes (10.5%), 2 cigars (5.3%) and 3 living with a smoker (7.9%). Of the 294 former smokers, 1 reported using NRT (0.3%), 6 electronic cigarettes (2.0%) 7 cigars (2.3%) and 6 living with a smoker (2.0%). The majority (95%) of former smokers had quit more than two years prior to interview.

Table 2 is a comparison of self-reported current cigarette smoking (yes/no) against biochemically-verified cotinine levels (high vs. low/no cotinine) used as the gold standard. Biochemical assays identified 13% (65/517) of patients as having high cotinine levels. Of these 65 patients, 38 self-reported being a current smoker (true positives), while 27 denied being a current smoker (false negatives), resulting in a sensitivity of 58%. Notably, high cotinine levels were detected in every patient who reported current smoking “some days”, and not “everyday”. Among the 452 patients who had low/no cotinine levels, all self-reported no current cigarette smoking (true negatives), resulting in 100% specificity. There were 0 false positives and 27 false negatives. The positive predictive value of self-reported cigarette smoking status was 100% and the negative predictive value was 94%.

Table 3 refines cotinine levels into three groups (high/low/no exposure) and shows how other self-reported sources of nicotine relate to these categories. Among the 517 patients, the prevalence of high, low, and no cotinine exposure was 13%, 54% and 33% respectively. In addition to current smoking, patients with high cotinine exposure reported current electronic

cigarette use, cigar use, and/or living with a current smoker. After accounting for these other sources of nicotine, the sensitivity was 82% (53 with reported exposure out of 65 with high cotinine levels). The 12 patients who denied all smoking-related exposure but had high cotinine levels included 10 self-reported former smokers (5 of whom quit within the last year (data not shown)) and 2 self-reported never smokers. One of the never smokers reported owning a bar in a state where indoor smoking is still permitted. These 12 misclassified patients were predominantly male (75%), white (83%) and had at least a college education (50%). Of the 279 patients with low cotinine levels, only 2% reported cigar smoking or living with a current smoker; the remaining 98% denied any other smoking-related exposure. Of the 33% of patients with no cotinine detected in their biospecimen, none reported any smoking-related exposure (100% specificity).

Discussion

To our knowledge, this is the first investigation to evaluate the association between self-reported smoking-related exposures and biochemically defined active, passive and no cotinine exposure among recently diagnosed NMIBC patients. Our study suggests that in a clinic setting, a single question: “Do you now smoke cigarettes every day, some days or not at all?” results in a suboptimal sensitivity of 58%. After taking account of cigars, electronic cigarettes and secondhand smoke exposure, the sensitivity was 82%. Nearly all patients with low cotinine levels denied exposure to any smoking-related source (98%). Our findings suggest that either biochemical verification or asking additional questions about smoking-related exposure are needed to accurately identify NMIBC patients who have smoking-related exposures and may benefit from tobacco treatment services. Indeed, the National Comprehensive Cancer Network (NCCN) Guidelines for Smoking Cessation recommend that all cancer patients are routinely asked whether they have smoked in the last 30 days and about other forms of tobacco use including pipes, cigars, smokeless tobacco and electronic cigarettes, nicotine replacement therapy, other forms of cessation medication, as well as smoking status of other household members[20].

A growing body of research suggests cancer patients are exposed to nicotine from other sources beyond cigarette smoking. In a study of 108 head and neck cancer patients, Alberg et al. determined the sensitivity of self-reported cigarette smoking increased from 61% to 76% when allowing for the possibility that secondhand smoke exposure or use of nicotine-containing products could have caused a positive cotinine test[21]. Warren et al. also found a high degree of misreporting among head and neck cancer patients undergoing surgery; 29.4% of smokers needed biochemical verification for accurate identification[10]. In a prior pilot study of NMIBC patients at our institution, we found the sensitivity of self-reported cigarette smoking was from 53%. The sensitivity was 77% after accounting for NRT use[8]. Our current study found only 7% of NMIBC patients self-reported current cigarette smoking, while nearly twice that number (13%) had high cotinine levels suggestive of active smoking exposure. Once other sources of nicotine exposure (including electronic cigarette use, cigar use, and secondhand exposure) were considered, the sensitivity was higher, at 82%. It is unknown why 19% (n=12) of our patients with high cotinine did not disclose any smoking-related exposure. Morales et al. found that cancer patients who claimed they had recently quit smoking were more likely than non-recent quitters to be misclassified[9]. This is

consistent with our finding that 5 of the 10 former smokers who misreported their exposure reported that they had quit smoking less than a year ago. There is also a growing awareness that nondisclosure of smoking status during medical visits is more common among patients who experience smoking-related stigma[22,23].

Cotinine is a reliable biomarker of recent nicotine exposure. Use of tobacco products such as cigarettes, pipes, cigars, smokeless tobacco, as well as secondhand smoking, nicotine replacement products and electronic cigarettes all result in detectable levels of cotinine. We used cut-points published by Goniewicz et al.[19] for urine and Benowitz et al. for saliva[6] to distinguish high (i.e., active) from low (i.e., passive) levels of exposure, and found different sources of nicotine exposure or polyuse in each category. More than half of the patients were classified as having low levels of cotinine exposure (54%). The sources of low cotinine exposure are not clear as only 2% of patients with low exposure reported living with a smoker or smoking cigars. Notably, the level at which biochemically-verified levels of nicotine exposure adversely impacts NMIBC recurrence risk is unknown. While nicotine is not a carcinogen, some animal studies suggest that nicotine promotes cell proliferation, angiogenesis, and epithelial to mesenchymal transition through nicotinic acetylcholine receptors found in the bladder, leading to enhanced tumor growth and metastasis[24].

Strengths of our study include its relatively large sample size and collection of self-report and biospecimen data on the same day. Limitations are acknowledged. We did not systemically collect information on cigars, pipes or smokeless tobacco. It is possible that the sensitivity could improve further if we had this additional information. Our study is comprised predominantly of older white men; therefore, our findings may not generalize to patients of other races and ages. The low proportion of women precluded us from performing analyses stratified by sex.

Conclusions

Our findings highlight the limitations of relying on a single question about current cigarette smoking. While biochemical verification identified more patients with substantial nicotine exposure than self-report, it carries considerable expense and only captures recent nicotine exposure. Our analysis provides evidence that a comprehensive assessment of tobacco related exposure (including cigarette smoking, recency, and other forms of nicotine use) should be used to more accurately classify patients in research studies and identify those that could be referred to tobacco treatment programs. Frequent screening appointments among NMIBC patients provide multiple opportunities for urologists to use these comprehensive assessments to encourage tobacco cessation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

DETER	Determinants of Bladder Cancer Recurrence Study
NMIBC	non-muscle invasive bladder cancer
NRT	nicotine replacement therapy
MSK	Memorial Sloan Kettering Cancer Center
NMIBC	non-muscle invasive bladder cancer
NRT	nicotine replacement therapy

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Table 1.

Characteristics of the study cohort.

	TOTAL n=517 (%)
Sex	
Female	110 (21.3)
Male	407 (78.7)
Race	
Asian	15 (2.9)
Black	12 (2.3)
White	460 (89)
Other	7 (1.4)
Missing	23 (4.4)
Married, living as married or in a relationship?	
Yes	451 (87.2)
No	64 (12.4)
Unknown	2 (0.4)
Education	
College or above	333 (64.4)
HS/Some college	172 (33.3)
Less than HS	10 (1.9)
Missing	2 (0.4)
Age at interview; median (minimum, maximum)	69 (19, 92)
Months since initial diagnosis, median (minimum, maximum)	14 (0, 53)
Stage at Initial Dx	
pTa	306 (59.2)
pT1	160 (30.9)
pTis	51 (9.9)
Grade at initial diagnosis	
Low	156 (30.2)
High	361 (69.8)
Self-reported cigarette smoking behavior at interview	
Current	38 (7.3)
Former	294 (56.9)
Quit less than two years ago	16 (5.4) *
Quit more than two years ago	278 (94.6) *
Never	185 (35.8)
Currently live with a smoker	
Yes	10 (1.9)
No	507 (98.1)

	TOTAL n=517 (%)
Currently use nicotine replacement therapy (NRT) **	
Yes	9 (2.7)
No	322 (97.0)
Missing	1 (0.3)
Currently use electronic cigarettes **	
Yes, Everyday	5 (1.5)
Yes, Somedays	5 (1.5)
No	321 (96.7)
Missing	1 (0.3)
Currently smoke cigars ***	
Yes	9 (1.7)
Unknown	508 (98.3)

* proportion among the 294 former smokers

** Among Ever smokers (current and former smokers)

*** Cigar smoking was not systematically collected, data collected from interviewer note

Table 2.

Comparison of biochemically-verified cotinine levels (high or low/no) against self-reported current cigarette smoking status

	High Cotinine N=65 (13%)	Low/No Cotinine N=452 (87%)	Total N=517
Self-Reported Current Cigarette Smoker Yes	38 (58%)	0	38 (7%)
Self-Reported Current Cigarette Smoker No	27 (42%)	452 (100%)	479 (93%)

Table 3.

Comparison of biochemically-verified cotinine levels (high, low or no) against different smoking-related sources

	High Cotinine N=65 (13%)	Low Cotinine N=279 (54%)	No Cotinine N=173 (33%)	Total N=517
Current cigarette smoker *	38 (58%)	0	0	38 (7%)
Current electronic cigarette user, no cigarettes **	6 (9%)	0	0	6 (1%)
Current cigar smoker only ***	6 (9%)	1 (<1%)	0	7 (1.5%)
Currently live with a smoker only	3 (5%)	4 (<2%)	0	7 (1.5%)
No reported nicotine exposure	12 (19%)	274 (98%)	173 (100%)	459 (89%)

* Of the 38 current smokers 8 also used NRT, 4 also used electronic cigarettes, 2 also used cigars, 3 live with a smoker

** Of the 6 electronic cigarette users, 1 also used NRT

*** Cigar smoking was not systematically collected, data collected from interviewer note