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ORIGINAL ARTICLE

Osteoporosis in colorectal cancer survivors: analysis of the linkage between SWOG trial enrollees and Medicare claims

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Abstract

Summary To explore the rates of osteoporosis (diagnosis and screening) and fractures in colorectal cancer survivors (CRCS), records of clinical trial enrollees was linked to Medicare. Female/male risk of fracture in CRCS is 74% higher than general population. Less than 30% of male and female CRCS receive osteoporosis screening. Osteoporosis is a significant morbidity in CRCS.

Introduction In the USA, the population of colorectal cancer survivors (CRCS) is on the rise. Calcium and vitamin D are the common thread between colorectal cancer and osteoporosis. We set to explore the patterns and prevalence of osteoporosis (OP) and osteoporotic fractures (OF) in CRCS who received fluorouracil-based therapy on SWOG trials.

Methods Data for CRCS from three SWOG phase III treatment trials between 1994 and 2000 ($N = 3775$) were linked to Medicare claims ($N = 1233$). OP was identified using ICD9 and HCPCS codes; OF was defined using a more restricted set of codes. We compared patterns of OP, OF, and screening for OP by gender in CRCS. Given the gender disparities in the rates of OP and OF, we used data from the National Health Interview Survey (NHIS) and the National Hospital Discharge Survey (NHDS) to assess the ratio of OF in females and males in general population.

Results Forty-seven percent of females and 15% of men CRCS had OP claims. Female CRCS were more likely than males to have OP (HR = 4.76 [3.77–6.01], $p < 0.0001$) and OF (HR = 2.64 [2.04–3.42], $p < 0.0001$). In the general population, the female to male ratio of OF was 1.67 as opposed to 2.90 in CRCS, indicating a significantly larger gender disparity of OF in CRCS ($p < 0.001$). Only 7% of men and 27% of women CRCS had OP screening.

Conclusion Despite a low rate of OP screening, the gender disparity of OF in CRCS is more pronounced than the general population. These findings provide an impetus for studying OP and OF in CRCS.

Keywords Osteoporosis · Colorectal cancer · Survivorship · Medicare claims · Gender disparity

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Background

Over the past two decades, the number of colorectal cancer survivors and duration of survivorship has risen dramatically. More than 1.5 million colorectal cancer survivors are alive in the USA; the majority will live as survivors with an unaltered life expectancy [1]. Although surveillance strategies for cancer recurrence are a focus of the early phase of cancer survivorship, there is a limited understanding of long-term complications of cancer and cancer-related therapies in this population [2].

Osteoporosis and osteoporotic fractures are a known complication of hormonal treatments in patients with breast and prostate cancer. For example, the prevalence of osteoporosis is 27% higher and the risk of fractures is 21% higher in breast cancer patients who use aromatase inhibitors (AI) than in the general population [3]. In men with prostate cancer on androgen deprivation therapy (ADT), the lifetime risk of fracture is 20% [4]. In order to reduce osteoporosis and osteoporotic fractures in these patients, professional societies have developed specific guidelines for the screening and treatment of bone health [5–8].

Currently, data regarding the prevalence of osteoporosis and osteoporotic fractures following a diagnosis of colorectal cancer is limited; however, there are reasons to believe that bone health may be affected in colorectal cancer survivors. Calcium and vitamin D are linked to both colorectal cancer incidence and the development of osteoporosis. Low intake and blood levels of calcium and vitamin D are linked to higher risk of colorectal cancers and increased risk of osteoporosis [9–12]. Low calcium and vitamin D also can impact the overall survival of colorectal cancer patients [13, 14]. In addition, the majority of colorectal cancer survivors are older than 60 years of age and thus at risk for many age-related complications including osteoporosis [2].

We explored rates of osteoporosis and osteoporotic fractures using a novel linkage between colorectal cancer patients enrolled in SWOG clinical trials and their Medicare billing claims. This linkage allowed the examination of a cohort of cancer patients who were treated and followed uniformly under protocol guidelines, combining the advantages of prospective staging and treatment data from trial records with long-term assessment of sequelae using Medicare claims.

Methods

To examine patterns of osteoporosis and osteoporotic fractures in colorectal cancer survivors, we pooled data from SWOG randomized phase III treatment trials S9304, S9415, and S9420 (Table 1) [15–17]. All 3 trials were designed to assess the significance of 5-FU delivery method and modulation on the survival of patients with colorectal cancer, and taken together, they showed how the use of infusional 5-FU resulted in lower toxicity than bolus 5-FU with no statistically detectable impact on survival. [15–17] Both S9304 and S9415 were conducted in patients with resectable colon or rectal cancer, while patients in S9420 had metastatic colorectal cancer. All three trials included 5-FU as part of their treatment.

SWOG subjects were linked to Medicare claims data according to Social Security number, sex, and date of birth. To enable a minimally sufficient amount of coverage time on Medicare to identify osteoporosis or osteoporotic fractures, only subjects with $\geq$ 12 months of continuous Medicare Parts A and B coverage at any time after registration to the SWOG trial were included. Subjects must simultaneously not have had HMO coverage for at least 12 months since Medicare claims are not available for individuals in an HMO. Because the required $\geq$ 12 months of Medicare coverage could have happened at any time after registration, patients may not have been $\geq$ 65 years old at randomization but could have aged into the Medicare claims cohort.

Osteoporosis was identified using ICD9 codes 733.00–733.03, 733.09, 733.90, and 733.99. Osteoporosis-related fractures were identified using ICD9 codes of 773.10–733.19, 733.81, 733.82, 733.93, 733.98, and 800.00–829.00. These codes are for pathological (i.e., non-traumatic) fractures and are most likely used to identify fractures related to osteoporosis. A systematic review of Medicare claims data by Curtis et al. supports that these codes should be included in the epidemiological evaluation of osteoporosis [18]. We also used the Healthcare Common Procedure Coding System (HCPCS) codes for capturing all fractures related to osteoporosis (Supplemental Table 1). Osteoporosis screening was identified using procedure codes specific to bone densitometry, as well as bone scan, given that bone metastasis and thus bone scan for evaluation of bone metastasis are rare in a colorectal cancer population (Supplemental Table 1) [19]. Osteoporosis and osteoporosis-related fractures were identified using any hospital claim, or $\geq$ 2 physician or outpatient claims at least 30 days apart, using HCPCS and ICD9 codes (Supplemental Table 1). To focus on the development of new cases of osteoporosis or related fractures, patients with evidence of pre-existing osteoporosis or fractures (prior to trial registration) were excluded from each respective analysis.

Two sets of comparisons were conducted. First, we compared patterns of osteoporosis and osteoporotic fractures by sex in patients with colorectal cancer. Second, we compared the difference in osteoporotic fractures by sex in colorectal cancer patients (using data from the SWOG treatment trials) to the difference in osteoporotic fractures by sex in the general US population (using data from the US general population). This comparison was conducted to evaluate whether potential sex disparities in osteoporotic fractures differed between cancer and non-cancer patients. Data from the 1994 National Health Interview Survey (NHIS) and the National Hospital

Table 1 Summary of SWOG Studies Included

Study ID	Publication title	Population	N original study			N linked to Medicare[1]		N included in this study[2]		N with osteoporosis claims	
			Total	Male	Female	Male	Female	Male	Female	Male	Female
S9304	Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144.	Rectal cancer patients with post-resection stage II or III.	1917	1241	676	489	253	445	226	67	108
S9415	Phase III SWOG 9415/intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole vs fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer.	Colon cancer patients with high-risk stage II or stage III.	1133	598	535	282	264	245	234	38	118
S9420	Assessment of infusional 5-fluorouracil schedule and dose intensity: a Southwest Oncology Group and Eastern Cooperative Oncology Group study.	Colorectal cancer patients with metastatic disease.	725	415	310	90	57	49	34	4	5

[1] Social Security number, sex, and date-of-birth match to Medicare records

[2] Social Security number, sex, and date-of-birth match to Medicare records; ≥ 12 months of Medicare coverage and no HMO coverage, anytime after SWOG registration

Discharge Survey (NHDS) were used to establish patterns of osteoporotic fractures by sex in the US general population [20, 21]. These two databases only include data on osteoporotic fractures, using a restricted set of ICD9 codes. Therefore, comparisons between colorectal cancer patients and the general population were limited to osteoporotic fractures only, rather than both osteoporotic fractures and osteoporosis diagnoses.

Statistical analysis

Baseline descriptive characteristics of SWOG participants were compared using *t* tests for continuous measures and chi-square tests for categorical measures.

Analysis comparing male to female colorectal cancer patients

To incorporate time from the beginning of observation until evidence of an event (osteoporosis and osteoporotic fracture), and to account for potential competing risks of death, we estimated the cumulative incidence from trial registration until identification of an event according to Medicare claims. Given that osteoporosis is more common in females, in order to estimate the strength of the association between sex and the different time-to-event outcomes, we used Cox regression [22]. Some participants experienced gaps in observation when Medicare coverage was discontinued temporarily for 3 months or longer (gaps < 3 months were ignored to allow for minor administrative switching between plans). Participant time-at-risk in Cox models includes only time under Medicare observation. All hazard ratios and *p* values were derived from multivariable models that included an adjustment for age at registration (< 65 vs ≥ 65), race (Black vs other), and BMI (continuous). A set of sensitivity analyses was performed, with metastatic patients (from study S9420) removed.

Analysis comparing risk of fracture by sex in cancer patients vs the general population

We also assessed whether patterns of osteoporotic fracture by sex differed between cancer patients and individuals in the US population. From both the NHDS and NHIS data, we calculated the ratio of the incidence rate per 1000 person years for females vs males. We specified the mean of these two sex risk ratios as the null hypothesis. In Cox multivariable regression, we tested whether the hazard ratio for fracture risk in SWOG colorectal cancer patients differed from the null hypothesis based on the US general population.

Results

Baseline characteristics of patients included in this analysis, as well as patients from these SWOG studies that were not included in the analysis, are reported in Table 2. No differences were observed between the men and women included in this analysis, with respect to age, race, or ethnicity. Those included in the analysis are significantly older than those not included, but there were no differences with respect to race or ethnicity.

Table 2 Descriptive characteristics of participants linked to Medicare claims

Characteristic	Male ($N = 739$)	Female ($N = 494$)	p value[1]	Not included in this analysis ($N = 2543$)	p value[2]
Baseline					
Age, median (range)	64 (36–86)	65 (25–86)	0.53	58 (18–89)	< 0.0001
Race, N (%)			0.07		0.18
Black	49 (7%)	51 (10%)		200 (7%)	
White	665 (90%)	428 (87%)		115 (5%)	
Other	25 (3%)	15 (3%)		2228 (88%)	
Ethnicity, N (%)			0.56		0.16
Non-Hispanic	712 (96%)	479 (97%)		2432 (96%)	
Hispanic	27 (4%)	15 (3%)		111 (4%)	
Post-baseline					
Osteoporosis and related fractures, N (%)			< 0.0001		
No	630 (85%)	260 (53%)			
Yes	109 (15%)	230 (47%)			
Osteoporosis screening, N (%)			< 0.0001		
No	691 (93%)	363 (73%)			
Yes	48 (7%)	131 (27%)			

[1] p value compares men to women, using t tests for continuous measures and chi-square tests for categorical measures

[2] p value compares those included in this analysis to those in the SWOG studies but not included in this analysis, using t tests for continuous measures and chi-square tests for categorical measures

Comparing male to female colorectal patients

Table 3 shows rates of osteoporosis, osteoporosis screening, and osteoporotic fractures for male and female colorectal cancer patients. Of note, a minority of both male and female colorectal cancer patients were screened for osteoporosis. Female colorectal cancer survivors were more likely than male survivors to be diagnosed with osteoporosis (HR = 4.76 [3.77–6.01], $p < 0.0001$), to be screened for osteoporosis (HR = 5.15 [3.74–7.09], $p < 0.0001$), and to be diagnosed with osteoporotic fracture using all applicable ICD9 codes (HR = 2.64 [2.04–3.42], $p < 0.0001$). Results were similar using a restricted set of ICD9 codes, to provide a comparison to the US general population (HR = 2.90 [2.14–3.93], $p < 0.0001$). These results were similar when patients with metastatic disease were excluded from the analysis; in the non-metastatic population only, female colorectal cancer survivors were more likely than male survivors to be diagnosed with osteoporosis (HR = 4.85 [3.83–6.14], $p < 0.0001$), to be screened for osteoporosis (HR = 5.15 [3.74–7.10], $p < 0.0001$), and to be diagnosed with osteoporotic fracture using all applicable ICD9 codes (HR = 2.68 [2.06–3.50], $p < 0.0001$) (Supplemental Table 2).

Comparing risk of fracture by sex in cancer patients vs the general population

Using NHIS data, the rate of fracture per 1000 person years was 4.6 for females and 2.8 for males, generating a sex risk ratio of 1.64. Using the NHDS data, the rate of fracture per 1000 person years was 21.3 for females and 12.5 for males, generating a sex risk ratio of 1.70 (i.e., 21.3/12.5), very similar to the ratio derived from the NHDS data (Fig. 1). We specified our null hypothesis as the mean of these two sex risk ratios, 1.67. The ratio of the risk difference in colorectal cancer survivors (2.90) to the risk difference in the general US cancer population (1.67) indicates that the fracture risk difference by sex is 74% greater in colorectal cancer survivors than in the general US cancer population (Fig. 1). A test of the hazard ratio for fracture risk in colorectal cancer patients (2.90) against the null hypothesis of 1.67 generated a p value < 0.001, indicating that the observed 74% increase in the difference in risk of fracture by sex was highly statistically significant.

Cumulative incidence of osteoporosis

Cumulative incidence of osteoporosis diagnoses by sex is plotted in Fig. 2, illustrating the dramatic difference between males and females in this population. The cumulative incidence rates for females vs males were 45% vs 12% at 5 years, 68% vs 22% at 10 years, and 83% vs 32% at 15 years.

Discussion

We found that female colorectal cancer survivors were 4.7 times more likely than male survivors to have claims for

Table 3 Association between sex and eventual osteoporosis diagnosis, screening for osteoporosis, and osteoporotic fractures

	Cox regression						
	No	Yes	5-year CI	10-year CI	Total CI	HR (95% CI)[1]	*p* value[1]
Outcome: osteoporosis diagnosis							
Sex							
Male	630	109	12%	22%	32%	Ref	
Female	260	230	45%	68%	83%	4.76 (3.77–6.01)	< 0.0001
Outcome: osteoporosis screening							
Sex							
Male	691	48	< 1%	3%	17%	Ref	
Female	363	131	2%	14%	63%	5.15 (3.74–7.09)	< 0.0001
Outcome: fractures (all ICD9 codes in Supplemental Table 1)							
Sex							
Male	648	91	10%	17%	27%	Ref	
Female	351	142	24%	39%	57%	2.64 (2.04–3.42)	< 0.0001
Outcomes: fractures (ICD9 codes 800.00–829.00)							
Sex							
Male	673	66	7%	12%	20%	Ref	
Female	381	112	19%	32%	47%	2.90 (2.14–3.93)	< 0.0001

[1] Odds ratios, hazard ratios, and *p* values are adjusted for age at baseline (< 65 vs ≥ 65), race (black vs other), and BMI (continuous)

osteoporosis and 2.6 times more likely to have claims for osteoporotic fractures. The risk difference for osteoporotic fractures between women and men with colorectal cancer was 74% higher than the risk difference between men and women in general population. It has been estimated that in the general population, about 1/3 of women and 1/5 of men over 50 years will experience osteoporotic fractures [23, 24]. Our findings for male colorectal cancer survivors were consistent with these estimates, but our findings for female colorectal cancer survivors were much greater (83% incidence at 15 years; Fig. 2). This suggests that the osteoporosis disparity by sex in colorectal cancer survivors is much greater and likely influenced by additional sex-related factors for females.

Other groups have reported an increased risk of osteoporosis in colorectal cancer survivors compared to non-cancer patients. In an analysis from the General Practice Research

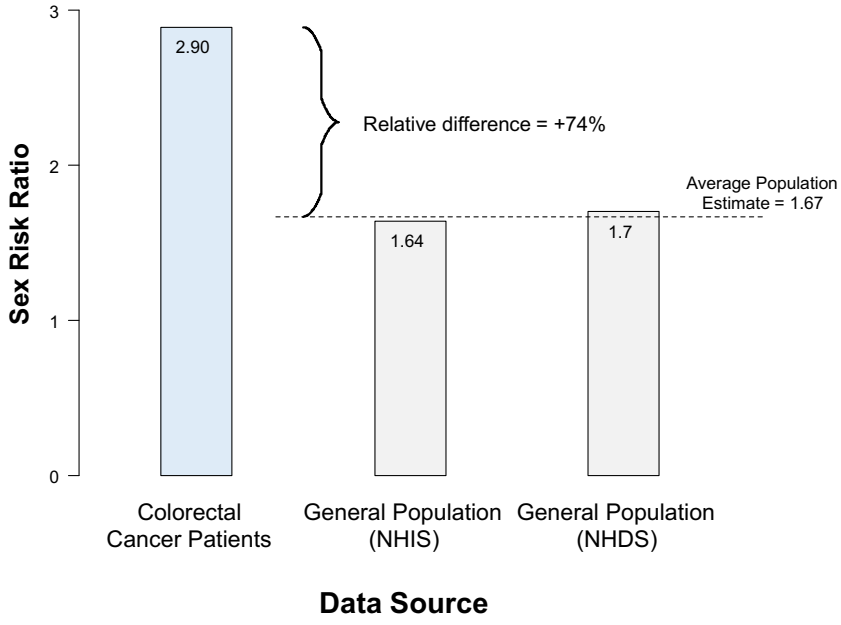


Fig. 1 The risk ratio for fracture per 1000 person years in colorectal cancer and general population. General population source is derived from two different sources, NHIS and NHDS

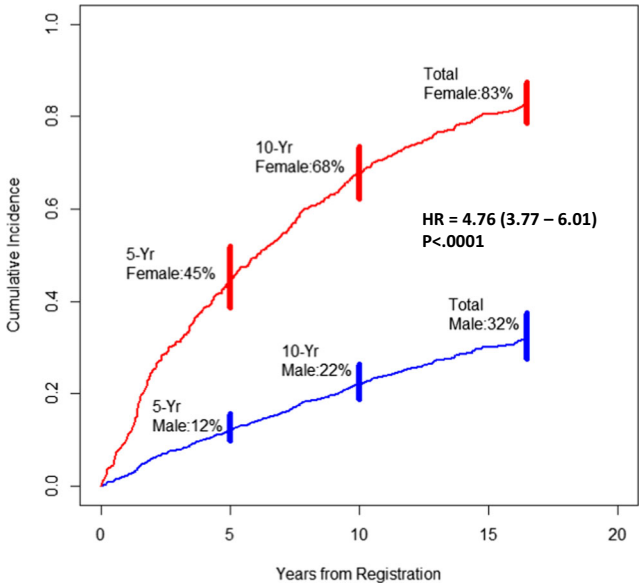


Fig. 2 Cumulative incidence of osteoporosis in females and males with colorectal cancer

Database in the UK, colorectal cancer survivors were compared to the general non-cancer population for their risk of osteoporosis. The definition of osteoporosis was based on diagnosis claims or bisphosphonate prescription codes. [25] The authors found that risk of osteoporosis was 40% higher in the colorectal cancer population compared to the non-cancer population, however, risk of osteoporotic fractures was not reported.

There are several factors that may explain the observed findings. First, calcium plays a significant role in both osteoporosis and colorectal cancer risk and its prevention. Calcium is important for bone health and low calcium intake is linked to osteoporosis [26, 27]. Concurrently, calcium plays a role in the development and progression of colorectal cancer via its interactions with the Wnt pathway [28, 29]. Calcium has been identified as a chemopreventive agent for colorectal cancer [30]. Calcium absorption happens in the proximal section of the small bowel, and thus, surgery for colorectal cancer has minimal impact, if any, on the absorption of calcium. Based on several dietary surveys in the USA, calcium intake is lower in women compared to men, thus putting women cancer survivors at higher risk of osteoporosis [31]. Furthermore, the impact of calcium intake on the reduction of colorectal cancer mortality in men and women is different [32]. Hence, differences in calcium intake and its interaction with colorectal cancer may play a role in the observed differences in osteoporosis between female and male colorectal survivors in our analysis.

Similarly, vitamin D plays a role in the development and progression of colorectal cancer [33]. Low vitamin D levels have been linked to both bone health and risk of several epithelial cancers—including colorectal cancers—and may link colorectal cancer and osteoporosis [34–36]. Secondary analysis of specimens of N9741 revealed that women compared to men with metastatic colorectal cancer have significantly lower plasma levels of 25(OH)D, an active metabolite of vitamin D [37, 38]. Therefore, dietary intake, as well as metabolism of vitamin D, may explain the observed difference in osteoporosis and osteoporotic fractures between men and women colorectal cancer survivors.

Hormonal influences in female colorectal cancer patients may play a role in the increased risk of osteoporosis. In other cancers, ovarian dysfunction and early menopause increase the risk of osteoporosis. While 5-FU is unlikely to cause permanent ovarian failure, it is possible that premenopausal women with rectal cancer who receive radiation are at an increased risk of ovarian failure and that the radiation may influence bone strength. Nonetheless, an exploratory comparison of osteoporosis and osteoporosis-related fracture in our population shows that osteoporosis diagnosis is higher in S9415 (colon cancer population) than it is in S9304 (rectal cancer population).

Although our study suggests a correlation between colorectal cancer and osteoporosis, the cause and effect between the two conditions is not established and it may be that osteoporosis increases the risk of colon cancer. Three retrospective studies suggest that colon adenomas are higher in subjects with osteoporosis [39–41]. In the study by Lim et al., women with osteoporosis had 60% higher risk of colon adenomas. Gowda et al. report that environmental factors such as smoking may be a confounder in the link between osteoporosis and colon adenoma. Our study excluded pre-existing cases of osteoporosis; however, it is possible that osteoporosis diagnosis that was not reflected in Medicare claims preceded the colorectal cancer diagnosis for some patients—especially women—complicating the interpretation of overall cause and effect.

Finally, it is possible that due to an increase in healthcare interactions, cancer patients are screened for osteoporosis more frequently than non-cancer patients. We found that female cancer survivors were over 5 times as likely to have a claim for bone mineral density than male cancer survivors. Osteoporotic fractures are usually symptomatic and do not need screening for diagnosis [42]. Therefore, our observation of higher rates of osteoporotic fractures in female colorectal cancer survivors is unlikely to be affected by the rates of screening.

Linkage between clinical trial data and claims is an opportunity to study the long-term consequences of cancer diagnosis and treatment-related complications. The strength of our study is patient and treatment homogeneity, novel comparison groups, and long-term follow-up from claims data. However, our study also has several limitations. First, this study represented a post hoc analysis; osteoporosis was not prospectively evaluated or followed in the study cohort, requiring instead a linkage to Medicare claims which may be limited due to the nature of claims databases, which are not designed for

research purposes. In particular, claims databases are not designed for research purposes and may be subject to misclassification, including the potential for underreporting of true rates of osteoporosis [43]. Although we have used the standard methods to properly identify osteoporosis using claims, we cannot verify the accuracy of the osteoporosis or osteoporotic fractures. Furthermore, due to the observational nature of the study, we cannot provide a mechanistic explanation for higher rates of osteoporosis in female colorectal cancer survivors. Additionally, given that our study population are Medicare beneficiaries and thus older, the significance of these findings in a younger cohort of colorectal cancer survivors is unknown. Finally, our results highlight disparities in osteoporosis and osteoporotic fractures by sex but do not explicitly show whether these disparities are due to the higher absolute incidence of events in females or lower absolute incidence of events in males with colorectal cancer compared to the general US population, or some combination thereof.

Our findings are hypothesis generating and should be confirmed in prospective studies. If confirmed, future studies exploring the mechanisms of osteoporosis and fracture risk should incorporate major risk factors for these conditions including age, family history, and prior fracture history. In the meantime, our claims data show that a minority of colorectal cancer survivors receive osteoporosis screening. Because osteoporosis and subsequent osteoporotic fractures are associated with high rates of mortality and morbidity, understanding populations at increased risk for osteoporosis can increase screening and treatment to prevent osteoporosis fractures.

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Compliance with ethical standards

Conflict of interest None.

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