The effects of oral and transdermal oestrogen replacement therapy on the risk of colorectal cancer: a focus on sensitivity analyses

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ABSTRACT

Objectives: To compare the effects of transdermal oestrogen and oral oestrogen replacement therapy on the risk of colorectal cancer and to conduct both deterministic and probabilistic sensitivity analyses to account for potential exposure misclassification.

Design: Data from a large, nested case-control study was analysed and cases of colorectal cancer diagnosed between 1992 and mid-1998 were extracted from the Saskatchewan Cancer Agency registry. Each case was matched on age to four controls using density sampling and information about HRT usage was obtained from the outpatient prescription drug plan database. Women were classified into oral and transdermal oestrogen users. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression and finally, the corrected odds ratios were computed after accounting for potential exposure misclassification.

Results: TDE usage was associated with lower risk of colorectal cancer (OR: 0.31; 95% CI: 0.13, 0.78) than OE (OR: 0.89; 95% CI: 0.76,1.04). The interpretation of these estimates did not change after accounting for potential misclassification of therapy route. These findings will support the decision making of physicians and women in choosing therapies that are most effective in reducing postmenopausal symptoms.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in Canada with approximately 24,800 incident cases and 9,600 deaths in 2021 (Statistics Canada 2021). Multiple studies have found a strong negative association between hormone replacement therapy (HRT) and incidence of colorectal cancer in older women and females with a lower BMI (Kampman et al. 1997, Prihartonoet al, 2000). In other studies, it was shown that the history of HRT use significantly reduces CRC mortality rate (Mandalson et al. 2003).

While multiple studies have explored metabolic and biologic differences between oral and transdermal HRT, little is known about the differences between the effects of oral oestrogen (OE) versus transdermal oestrogen (TDE) therapy on incidence of CRC. In some studies, the use of HRT in a transdermal form resulted in greater protection, however they are susceptible to unmeasured or unadjusted biases. In this report, we use a specific subset of data set analyzed in Csizmadi and colleague's study (2004) to find the effect of OE and TDE therapy on CRC, use sensitivity analysis to account for potential misclassification of exposure, and investigate if TDE still offers greater protection after accounting for exposure misclassification.

METHODS

Study design

This report used a subset of data from Csizmadi and colleagues' study (2004), a large population-based nested case control study that investigated the effects of OE and TDE on the risk of CRC among menopausal and peri-menopausal women in Saskatchewan, a Canadian province. The original dataset was obtained from Saskatchewan Health's (SH) electronic databases that store health information of over 99% of the province's population. 91% of those included in the databases are eligible for outpatient drug prescription benefits, while the majority of those who are not are mostly First Nations who receive these same benefits under a federal program (Downey et al, 2000).

Study subjects

The data was extracted from the Saskatchewan Cancer Agency (SCA) and women were eligible for participation if they were 50 years or older and diagnosed with colorectal cancer through a histologic exam between January 1, 1981 and June 30, 1998. The SCA is one of the largest and most accurate cancer registries in Canada because cases are identified using both pathology reports and physician service claims. Patients, both cases and controls, were eligible if they had been registered in the SH for at least 5 years, eligible for outpatient prescription drug benefits, and had no previous cancer diagnosis (in exception of nonmelanoma skin cancer and cancer of the cervix in situ) prior to the index date. SCA was used to verify if participants were not diagnosed with cancer.

Each colorectal cancer case was matched with four controls on (±1) year of birth; and controls had to have been living in Saskatchewan at the case's index date (diagnosis date). For each case, 16

potential controls from the SH were randomly sampled using incidence density sampling, with replacement, from all eligible controls. They were then screened for any history of cancer prior to the case's index date using SCA and participants who had a cancer diagnosis were excluded as potential controls. Among women who had no histories of cancer prior to the case's index date, four controls were randomly sampled without replacement. Women were classified according to their history of HRT use: TDE use only; OE use only; or use of TDE or OE without exclusion of women who may have used both OE and TDE (Csizmadi et al. 2004).

Statistical analysis

Conditional logistic regression was fitted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the 3 exposure classifications. The effect of age as a confounder was adjusted for with matching. Other potential confounders such as NSAID use in years before the index date, ever use of prescription drugs, frequency of doctor visits etc. (see Table 3) were assessed, but none had a significant effect on the odds ratios. All oestrogen exposure categories were calculated with the exclusion of exposure during the 2 years prior to index dates (Csizmadi et al. 2004). The backward and forward selection model selection methods were used to identify the best regression model which met all the model assumptions after diagnostic tests. All statistical analyses were carried out using the R software (version 4.2.0).

Sensitivity Analysis

The identification of women as having been exposed, or an 'ever' user, was if she had received at least one prescription of OE or TDE at least 2 years prior to the index date. Oestrogen exposure was ascertained by dispensing data from the records of the Saskatchewan Health outpatient prescription drug plan database. The type of formulation, strength, and number of units dispensed were obtained for each woman from the time her drug prescription coverage began, until the date of colorectal cancer diagnosis for cases or assigned index dates for controls.

This use of administrative claims to classify exposure in our best model is superior to self-reported medication use in that it reduces recall bias, however it is still susceptible to bias when the pharmacy claims do not reflect the actual use of the medication by the patients. The exposure variables assume that if a woman received a prescription for OE or TDE, then they were 100% compliant. The reality is that prescriptions may have been filled, but the women may have 1) never taken it, 2) discontinued it, or 3) used the prescription intermittently. Consequently, there is a

concern that the cases and controls do not reflect the true measurements and that this may have affected the odds ratios of colorectal cancer risk for both OE and TDE. Therefore, both deterministic and probabilistic sensitivity analyses were conducted using external literature on the rates of adherence to transdermal HRT and oral HRT to try and quantify the effect this differential exposure misclassification bias has on our best model estimates.

Deterministic Bias Analysis

The bias parameters used to conduct the sensitivity analysis for exposure misclassification are sensitivity and specificity, estimated by external literature. Using a study evaluating the compliance over three years to hormone replacement therapy in menopausal women controlled in a third level academic center, it was found that 56 of 123 women on oral oestrogen dropped treatment and 38 of 179 women on transdermal oestrogen dropped treatment. From this, we calculated discontinuity rates of 45.5% and 21.2% for oral and transdermal oestrogen hormone replacement therapy users (Cano 1994).

Sensitivity is calculated as the proportion of exposed subjects who are truly exposed: True positive/ (True positive + False Negative). Specificity is defined as the proportion of unexposed subjects who are classified as being unexposed: True Negative/ (True Negative + False Positive). Table 1 below shows the methods used to calculate the expected true data given the observed data with exposure misclassification.

Table 1: Calculating expected true data given the observed data with exposure misclassification.

	Truth		Expected observed	
	E_1	E_0	E_1	E_0
D_+	A	B	$a = A(\mathrm{SE}_{D+}) + B(1 - \mathrm{SP}_{D+})$	$b = A(1 - \mathrm{SE}_{D+}) + B(\mathrm{SP}_{D+})$
D_-	C	D	$c = C(\mathrm{SE}_{D-}) + D(1 - \mathrm{SP}_{D-})$	$d = C(1 - \mathrm{SE}_{D-}) + D(\mathrm{SP}_{D-})$
Total	$A + C$	$B + D$	$a + c$	$b + d$

In the study design, exposure to HRT during the 2 years prior to index dates was not included in exposure calculations, because of evidence suggesting that women who begin to feel unwell as a result of undiagnosed cancer may discontinue HRT, leaving primarily healthy women as HRT users (Csizmadi et al. 2004). Given this, we justify that there would be no differential rates of discontinuity between cases and controls and thus we use the same rates within each formulation

type. Thus, we are interested in the sensitivity of each exposure among the cases and controls: SE_{D+} / SE_{D-} . Using the discontinuity rates, the SE_{D+} / SE_{D-} was 54.5% for oral oestrogen exposure and 78.8% for transdermal oestrogen exposure. We used a specificity of 100% for each exposure, indicating that the entire proportion of non-HRT users were correctly classified as being unexposed. This is again justified by the use of prescription claims for measurement of exposure, as hormone replacement therapy is not available to purchase over the counter. With the sensitivity and specificity, the expected observed number of subjects in the OE and TDE categories was calculated (Table 2).

Table 2. Observed and expected data with exposure misclassification using external literature.

	Observed		Expected	
	ORAL	**TRANSDERMAL**	**ORAL**	**TRANSDERMAL**
CASES	248	5	$248(54.5\%) = \mathbf{135}$	$5(78.8\%) = \mathbf{4}$
CONTROL	1057	62	$1057(54.5\%) = \mathbf{576}$	$62(78.8\%) = \mathbf{49}$

Using the *episenr* package in R, the *misclassification* function used the fixed bias parameters of sensitivity and specificity to calculate a misclassification bias corrected relative risk and odds ratios with a 95% confidence interval.

Probabilistic Sensitivity Analysis

In addition to the simple bias analysis, we also conducted a probabilistic bias analysis (PBA). This assigns distributions to the sensitivity bias parameter we indicated in the deterministic analysis rather than specifying one set of parameters. The simple bias analysis assumes the parameters are known without error, so the PBA will attempt to account for the variation in the discontinuity rate found across other studies. Other literature values for discontinuity rates included 21% and 61% for OE, and 28.8% and 69% for TDE (Erenus et al. 1999, Ettinger et al. 1999). These rates along with those specified above were used to set the range of sensitivity: 39% - 72% for OE and 31% - 78.8% for TDE. We parameterized triangular probability density functions with the minimum and maximum values of these ranges, and with the mode equal to the average of the ranges. As

described above, we only used a specificity of 1 with no range. When attempting to set a theoretical range for specificity, we did not gain a distribution as many of the re-classified simulations obtained negative values and therefore 'NA' odds ratios. This is likely due to the very small sample size for transdermal oestrogen users.

The *probsens* function within the R *episenr* package was used. This utilizes Monte Carlo sampling techniques to generate a frequency distribution of corrected estimates of effect from the given probability distributions for the bias parameters. In Monte Carlo sampling, bias parameter values are chosen from the probability distribution specified, and then these chosen values are used to conduct a single simple bias analysis. This process was then repeated 200000 times, each time sampling a set of bias parameters and correcting the estimate of the odds ratio; yielding the median of the odds ratios and a 95% confidence interval for oral and transdermal oestrogen exposures individually.

RESULTS

A total of 6,177 participants were included in the study of which 1261 were identified as cases who had historically confirmed colorectal cancer, and 4916 age-matched controls for the cases. **Table 3** shows the health-related characteristics of the study population according to colorectal cases and controls. The mean age for both cases and controls was 74.1 years (SD: 10.3). There was no difference in prescription drug use, however, a greater percentage of the cases (64.1%) had over 15 frequent hospital visits in the year before the index date compared to the control group (28.7%). A significant difference was observed between the cases and controls for having a sigmoidoscopy 1-2 years before the index date (70.8% vs 4.7%).

Table 3. Health-related Characteristics of colorectal cancer cases and control.

	Total (n=6177)	Cases (n=1261)	Controls (n=4916)
Age, years at index date			
Mean (SD)	74.1 (10.3)	74.1 (10.3)	74.1 (10.3)
Median [Min, Max]	75.0 [50.0, 101]	75.0 [50.0, 101]	75.0 [50.0, 101]
Age Group, years at index date			
50-69	1651 (26.7%)	338 (26.8%)	1313 (26.7%)
70-89	3540 (57.3%)	723 (57.3%)	2817 (57.3%)
90+	986 (16.0%)	200 (15.9%)	786 (16.0%)
NSAIDS use in years before the index date			
1-5	3385 (54.8%)	623 (49.4%)	2762 (56.2%)
6-10	3483 (56.4%)	663 (52.6%)	2820 (57.4%)
11-15	3594 (58.2%)	710 (56.3%)	2884 (58.7%)
Ever use of presciprtion drugs prior to index date			
Cardiovascular drugs	4102 (66.4%)	855 (67.8%)	3247 (66.0%)
Central nervous system drugs	4482 (72.6%)	891 (70.7%)	3591 (73.0%)
Other hormones and substitutes	2446 (39.6%)	477 (37.8%)	1969 (40.1%)
Vitamins	1124 (18.2%)	223 (17.7%)	901 (18.3%)
Ever Use of Oral contraceptives	94 (1.5%)	21 (1.7%)	73 (1.5%)
Frequency of doctor visits in year before index date			
0-2	1025 (16.6%)	40 (3.2%)	985 (20.0%)
3-7	2221 (36.0%)	88 (7.0%)	1287 (26.2%)
8-14	1375 (22.3%)	325 (25.8%)	1231 (25.0%)
15+	1556 (25.2%)	808 (64.1%)	1413 (28.7%)
Frequency of doctore visits 2-5 years before index date			
0-9	809 (13.1%)	170 (13.5%)	639 (13.0%)
10-24	1266 (20.5%)	259 (20.5%)	1007 (20.5%)
25-59	2459 (39.8%)	531 (42.1%)	1928 (39.2%)
60+	1643 (26.6%)	301 (23.9%)	1342 (27.3%)
History of Sigmoidoscopy Year before the index date			
1-2 years before index date	1125 (18.2%)	893 (70.8%)	232 (4.7%)
3-5 years before index date	406 (6.6%)	92 (7.3%)	314 (6.4%)

The associations between colorectal cancer and HRT usage are also presented (Table 4). For women who had used both oral and transdermal, the OR was 0.82 (95% CI: 0.51, 1.31) which was not statistically significant. No bias analysis was conducted for women in the both OE and TDE exposure category given the limited information about the use of both in the literature. For women that used TDE only, the uncorrected age-adjusted OR (0.31; 95% CI: 0.13, 0.78) is the equivalent to the deterministically corrected OR which had a wider 95% confidence interval (95% CI: 0.12, 0.78). Among women who used OE only, the age-adjusted OR was not significant (OR=0.89; 95% CI: 0.76, 1.04). The interpretation of the results for the odds ratio of TDE use only and OE use only was unchanged after accounting for exposure misclassification in a deterministic and probabilistic bias analysis.

Table 4. Uncorrected, and corrected odds ratios with 95% confidence intervals for incidence of colorectal cancer among postmenopausal oestrogen users.

	Uncorrected age-adjusted OR		Deterministic corrected OR		Probabilistic corrected OR	
	OR	95% CI	OR	95% CI	OR	95% CI
Transdermal use Only	0.31	0.13, 0.78	0.31	0.12, 0.78	0.31	0.12, 0.82
Oral oestrogen use only	0.89	0.76, 1.04	0.87	0.71, 1.05	0.87	0.57, 1.32
Both Transdermal and Oral oestrogen use	0.82	0.51, 1.31	-	-	-	-

DISCUSSION

Multiple studies have shown a protective effect of oestrogen replacement therapy on colorectal cancer risk; with most of them finding more protection against CRC amongst the TDE users. The effect of oral and transdermal therapy obtained in this report is comparable to that of other previous studies and our sensitivity analysis of potential exposure misclassification did not dramatically change the direction and magnitude of effects.

In our best model, TDE use showed a larger decrease in the odds of colorectal cancer than OE. Since we expect that the transdermal route offers easier administration, and therefore higher adherence, there was concern that the observed cases and controls did not reflect the true measurements. Additionally, the ascertainment of exposure in the data assumes that if a patient

had filled a prescription, they were 100% compliant, which is very unlikely. Therefore, a sensitivity analysis to correct for differential exposure misclassification was warranted.

To correct for exposure misclassification, the most common treatment discontinuity rates were found in the literature and applied to our original data, under both deterministic and probabilistic approaches, to obtain new estimates had misclassification not occurred. After accounting for exposure misclassification, TDE still had a better protective effect against CRC under both sensitivity analysis methods. The OR for OE stays virtually the same after sensitivity analyses and although TDE shows better protection compared to pre-analysis, the effect is minimal. This suggests that the effect of discontinuing or not complying to prescriptions is negligible in this analysis.

The use of NSAIDs, vitamins, oral contraceptive, and frequency of doctor visits prior to index date had a negligible impact on ORs, so the final model did not include any of these covariates. Additionally, one may argue that diet and physical activity may confound the relationship between HRT modes and CRC; however, a minimal impact of these covariates on CRC has been shown by other studies (Grodstein et al, 1998; Prihartono et al, 2000). To our knowledge, no specific health-related differences exist between women who use OE and TDE. Additionally, we ruled out socioeconomic status is a confounder of the effect of replacement therapy to CRC since TDE was under unrestricted coverage access during the study period (Csizmadi et al. 2004).

Although our report accounts for potential exposure misclassification and still finds similar effects as previous studies, it has some limitations. First, there was a small number of cases who used TDE. There is, however, a sufficient number of controls and if the TDE is truly as protective as it was suggested in this report, the number of cases should be very small. Although most of our results were significant, a much larger study with more cases exposed to TDE is warranted to confirm these effects. Another limitation is that the literature on prescription discontinuity rates among OE and TDE users is scarce. A total of 3 studies were used to specify the range of sensitivity bias parameters. Had there been more evidence available, we would suggest using a triangular or trapezoidal distribution calculating the mode as an inverse variance weighted average or a uniform distribution to specify the same likelihood of each value within the range. While discontinuity rates were the best estimate of adherence to treatment available, it does not fully capture the true use – for example, some women may have continued their treatment but were taking it inappropriately.

Although the effect of HRTs on CRC was still negligible even after using more extreme discontinuity rates, more evidence is needed to understand the behaviors of women using oral or transdermal route or both.

A notable strength of our report is that the data about exposure and cancer diagnosis was very accurate and was representative of the study population due to a meticulous data collection procedure adopted in SCA and SH, from which the data used in this study was extracted. For this reason, the estimates obtained are less likely to suffer from selection bias and exposure misclassification, as was proven by both deterministic and probabilistic quantitative bias approaches.

CONCLUSION

To conclude, TDE offers a better protection against the risk of colorectal cancer among menopausal women than OE. After correcting for potential misclassification of exposure, this relationship remains the same. Although this effect has been known for a few years now, it is imperative to investigate new potential sources of bias in studies to allow up-to-date results. Knowledge about which therapy is most effective to reducing the risk of cancer will help physicians choose the most appropriate therapies for their patients to minimize their postmenopausal symptoms.

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