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Smoking and Smoking Cessation in Relation to Mortality

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Abstract

Context—Smoking causes death in many ways, but the rate of risk reduction after quitting, compared to continuing to smoke, is uncertain. There is inadequate or insufficient evidence to infer the presence or absence of a causal relationship between smoking and ovarian cancer and colorectal cancer.

Objective—To assess the relation between cigarette smoking and smoking cessation on total and cause-specific mortality in women.

Design, Setting, and Participants—Prospective observational study of 104,519 female participants in the Nurses' Health Study followed from 1980 to 2004.

Main Outcome Measure—Hazard ratios for total mortality, further categorized into vascular and respiratory diseases, cancers and other causes.

Results—A total of 12483 deaths occurred in this cohort, 4485 (35.9%) among never smokers, 3602 (28.9%) among current smokers, and 4396 (35.2%) among past smokers. Compared to never smokers, current smokers had an increased risk of total mortality (hazard ratio = 2.81, 95% confidence interval (CI) = 2.68–2.95) and all major cause-specific mortality evaluated. The hazard ratio for cancers classified by the 2004 Surgeon General's report to be smoking-related was 7.25 (CI:6.43–8.18) and for other cancers, 1.58 (CI:1.45–1.73). The hazard ratio for colorectal cancer was 1.63 (CI: 1.29–2.05) for current smokers and 1.23 (CI:1.02–1.49) for former smokers, compared to never smokers. A significant association was not observed for ovarian cancer. Significant trends were observed for earlier age at initiation for total mortality (P=0.003), respiratory disease mortality (P=0.001), and all smoking-caused cancer mortality (P=0.001). The excess risk for all-cause mortality decreases to the level of a never smoker 20 years after quitting, with different timeframes for risk reduction observed across outcomes. Approximately 64% of deaths among current smokers and 28% of deaths among former smokers were attributable to cigarette smoking.

Conclusions—Most of the excess risk of vascular mortality due to smoking can be eliminated rapidly upon cessation and within 20 years for lung diseases. Postponing the age of smoking initiation has a dramatic impact on risk of respiratory disease, lung cancer, and other smoking-caused cancer deaths and little effect on other cause-specific mortality. These data suggest that smoking increases the risk of colorectal cancer mortality but not ovarian cancer mortality.

Statistical Analysis

Person-years of follow-up accrued from the date of return of the 1980 questionnaire until either the date of death or the end of follow-up (1 June 2004), whichever came first. We started follow-up in 1980 since alcohol use and physical activity were not ascertained until this follow-up cycle. Person-time for each 2-year follow-up period was equal to the number of months between the return of successive questionnaires. Women did not contribute person-time in follow-up cycles in which they were missing smoking data.

We evaluated the effect of cigarettes smoked per day, age at starting smoking, and time since quitting smoking on total and cause-specific mortality. We also present data on pack-years of smoking in a supplementary table, if readers are interested. We also chose to evaluate cancers not classified by the 2004 Surgeon General's report to be smoking-related if more than 300 cancer-specific deaths were available. Lastly, we evaluated birth cohort effects in our population by evaluating the hazard ratios for those born between 1920–1929 and 1930–1939, excluding deaths before age 56. We used never smokers as the reference group for the analyses evaluating the hazard ratios (HRs) for cigarettes smoked per day and age at initiation among current smokers, and current smokers as the reference group for the analysis evaluating the HRs for time since quitting among former smokers.[8] For all analyses, we used Cox proportional hazard models conditioned on age in months and follow-up cycle. All multivariate models included history of hypertension, diabetes, and high cholesterol levels, body mass index, change in weight from age 18 to baseline, alcohol intake (categories of non-drinkers and drinkers of 0.1–4.9, 5.0–14.9, and 15.0+ grams/day), physical activity (quintiles based on intensity level and a metabolic equivalent task (MET) value calculated from the specific activity engaged in most frequently (1980–1984) and MET hours/week (1986–2000), previous use of oral contraceptives (never-, past-, current-user), postmenopausal estrogen therapy (never-, past-, current-user) and menopausal status, and parental history of myocardial infarction before age 65 years. We also additionally adjusted for servings of beef, pork, or lamb, servings of processed meat, total calcium and folate intake, and duration of aspirin use when evaluating the relation between smoking and colorectal cancer mortality. All variables except for height were updated biennially until diagnosis of non-fatal disease. Tests for linear

participant started smoking, using the Wald test. The exposed attributable fraction was calculated using the hazard ratios for current or former smokers compared to never smokers.

For all analyses, we excluded participants with a prior history of cancer (other than non-melanoma skin cancer), vascular disease, or respiratory disease before baseline. We also excluded those participants (n=1,872) who had smoked but did not provide their age at smoking initiation. There were 104,519 participants included in the analyses of number of cigarettes smoked per day and smoking cessation, and 79,172 participants included in the analyses of age at start of smoking, as that included only current and never smokers. All analyses were conducted using SAS software, version 9 (SAS Institute Inc, Cary, NC). All P values were based on 2-sided tests and were considered statistically significant at $P \leq .05$.

Smoking and smoking cessation in relation to mortality

Table 3

Total and Cause-specific Mortality by Age at Starting Smoking among Current Smokers in the Nurses' Health Study, 79,172 women followed from 1980 to 2004*

		Age at Starting among Current Smokers				
	Never Smoker	<=17 years	18 to 21	22–25	26+	*P* for trend
Total Mortality						
Person-yrs (%)	1076636 (71.9)	92386 (6.2)	262856 (17.6)	43366 (2.9)	22152 (1.5)	
Deaths: 8087	4485	746	2194	463	199	
A-Ad Hazard Ratio†	1.00	3.00 (2.78, 3.25)	2.75 (2.61, 2.90)	2.70 (2.45, 2.98)	2.30 (1.99, 2.65)	<0.001
M-V Hazard Ratio‡	1.00	2.93 (2.70, 3.18)	2.83 (2.67, 2.99)	2.79 (2.52, 3.07)	2.40 (2.08, 2.78)	0.003
Total Vascular Disease (includes coronary heart disease and cerebrovascular disease)						
Deaths: 1980	1073	190	517	133	67	
A-Ad Hazard Ratio	1.00	3.40 (2.91, 3.98)	2.80 (2.51, 3.11)	3.11 (2.59, 3.73)	3.09 (2.41, 3.97)	0.56
M-V Hazard Ratio	1.00	3.61 (3.06, 4.24)	3.15 (2.82, 3.53)	3.49 (2.90, 4.21)	3.44 (2.67, 4.42)	0.84

* Reference category consists of never-smokers. All covariates including smoking updated until diagnosis of disease.

† Age-adjusted relative risk. Ninety-five percent confidence intervals are shown in parentheses.

‡ Adjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy and menopausal status, parental history of myocardial infarction before age 60 years, and daily number of cigarettes smoked. Multivariate hazard ratios shown reflect the hazard for current smokers smoking a pack of cigarettes (20 cigarettes) per day compared to the hazard for a never smoker.

Non-steroidal anti-inflammatory drugs and the risk of *Clostridium difficile*-associated disease

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Increasing age, length of hospital stay and previous antibiotic use have been established as important risk factors in the development of *Clostridium difficile* associated disease (CDAD). Several case reports over the past 30 years have linked diclofenac, a non-steroidal anti-inflammatory drug (NSAID) with CDAD. We assessed whether NSAID use in general, and diclofenac use in particular, is associated with an increased risk of CDAD.

WHAT THIS STUDY ADDS

- In this population based study, the use of diclofenac was associated with a 35% increase in the risk of developing CDAD. This association persisted when we limited the analysis to non-hospitalized patients. No association was found between the use of any other NSAIDs and the risk of CDAD.

AIM

Several case reports have linked diclofenac, a non-steroidal anti-inflammatory drug (NSAID), with *Clostridium difficile* associated disease (CDAD). We assessed whether NSAID use in general, and diclofenac use in particular, is associated with an increased risk of CDAD.

METHODS

We used the United Kingdom's General Practice Research Database (GPRD) to conduct a population-based case–control study. All cases of CDAD occurring between 1994 and 2005 were identified and were matched to 10 controls each. Conditional logistic regression was used to estimate the odds ratio of CDAD associated with current NSAID use, adjusting for covariates.

RESULTS

We identified 1360 CDAD cases and 13 072 controls. We found an increased risk of CDAD associated with diclofenac (adjusted odds ratio (OR) 1.35, 95% confidence interval (CI) 1.10, 1.67). We did not observe an increased risk of CDAD with use of any other NSAID. No dose–response for diclofenac exposure was found. When we analyzed only patients who were not hospitalized in the year before the index date, we found diclofenac to have a similar effect on CDAD risk (Adjusted OR 1.43, 95% CI 1.11, 1.84).

CONCLUSION

Diclofenac use is associated with a modest increase in the risk of CDAD. In patients at risk of CDAD, other NSAIDs could be prescribed.

Case definition

Cases of CDAD were defined as having a first clinical diagnosis of CDAD, a first laboratory diagnosis of CDAD or a first prescription of oral vancomycin, its only indication being CDAD [13], between January 1 1994 and December 31 2005. Only first events were included as cases to ensure that the patient was not being treated for a recurrence of CDAD [2, 14]. The index date for included cases was the date of their first CDAD event. Cases had to be aged 18 years or older and have at least 2 years of records in the GPRD prior to the date of diagnosis to be entered into the study.

Control selection

For each case, up to 10 controls (both cases and controls were aged 18 years and older) were randomly selected from patients attending the same medical practice as the case, matched on age ±2 years), who had not received a prescription for oral vancomycin and were neither toxin positive nor had a clinical diagnosis of *C. difficile* recorded by the time the case was diagnosed (index date). We matched on medical practice to control for possible physician-related or practice related recording differences and geographical variation in the exposure.

Statistical analyses

The primary analysis was based on conditional logistic regression to obtain an odds ratio which can be interpreted as an estimate of the rate ratio of CDAD with regards to NSAID use. Patients were classified as currently exposed to NSAIDs if they received a prescription for any NSAID in the 90 day period prior to the index date, in order to capture both constant and intermittent use of these agents almost exclusively prescribed for inflammatory pain relief, otherwise they were considered unexposed.

The adjusted odds ratio of CDAD was estimated for current use of all NSAIDs after adjustment for gender, co-morbidities and co-prescriptions. The secondary analysis used conditional logistic regression to evaluate the association between current use of individual NSAIDs and development of CDAD. Furthermore, a dose–response analysis was performed using the number of prescriptions for each NSAID in the 180 day period prior to the index date, among current users. We defined the dose–response exposure measure based on its distribution as either less than five or more than five prescriptions in the 180 days prior to the index date.

Finally, a sensitivity analysis was performed to assess the effect of hospitalization in the year prior to the index date. All analyses were performed using SAS statistical software, version 9.1.3.

	Cases	Controls	*P* value
Number of subjects	1 360	13 072	
Gastro-intestinal diseases in the 2 years prior to the index date			
Acid reflux	78 (5.7%)	475 (3.6%)	0.0001
Inflammatory bowel disease	67 (4.9%)	73 (0.56%)	<0.0001
Diverticular disease	53 (3.9%)	345 (2.6%)	0.0070
Gastrointestinal bleeding	44 (3.2%)	128 (0.98%)	<0.0001
Peptic ulcer	3 (0.22%)	18 (0.14%)	0.45
Other diseases any time prior to the index date			
Cancer	60 (4.4%)	234 (1.8%)	<0.0001
Chronic obstructive pulmonary disease	133 (9.8%)	542 (4.2%)	<0.0001
Congestive heart failure	158 (11.6%)	596 (4.6%)	<0.0001
Dementia	43 (3.2%)	244 (1.9%)	0.0011
Diabetes	150 (11.0%)	1 055 (8.1%)	0.0002
Heavy alcohol consumption	22 (1.6%)	94 (0.72%)	0.0004
Liver failure	5 (0.37%)	15 (0.11%)	0.017
Myocardial infarction	49 (3.6%)	221 (1.7%)	<0.0001
Renal failure	71 (5.2%)	145 (1.1%)	<0.0001
Stroke	59 (4.3%)	267 (2.0%)	<0.0001
Medications in the 90 days prior to the index date			
Any antibiotic	681 (50.1%)	2 218 (17.0%)	<0.0001
Any H_2-receptor blocker	86 (6.3%)	515 (3.9%)	<0.0001
Any proton pump inhibitors	356 (26.2%)	1 463 (11.2%)	<0.0001
Oral corticosteroids	3 (0.22%)	5 (0.04%)	0.0065

Table 1 Clinical characteristics of cases and controls

Table 3

Crude and adjusted odds ratios of CDAD associated with NSAID exposure in the 90 days prior to the index date

NSAIDS exposure in the 90 days prior to the index date	Cases	Controls	Crude OR	Adjusted* OR	95% CI
Any traditional NSAID	462 (34.0)	3 709 (28.4)	1.27	0.97	0.86, 1.10
Diclofenac	96 (7.1)	547 (4.2)	1.63	1.35	1.10, 1.67
Ibuprofen	42 (3.1)	446 (3.4)	0.91	0.85	0.62, 1.15
Naproxen	12 (0.88)	108 (0.83)	1.06	0.99	0.56, 1.75
Other traditional NSAIDs	38 (2.8)	262 (2.0)	1.36	1.10	0.79, 1.51
Cox-2 inhibitors	11 (0.81)	116 (0.89)	0.92	0.77	0.42, 1.39
Acetylsalicylic acid	319 (23.5)	2 656 (20.3)	1.18	0.88	0.77, 1.01

*Adjusted for gender, comorbidities, prescription of antibiotics, H_2-receptor antagonists, proton pump inhibitors and oral steroids.

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Breastfeeding is Associated with Improved Child Cognitive Development: A Population-Based Cohort Study

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Objective To assess the association between breastfeeding and child cognitive development in term and preterm children.

Study design We analyzed data on white singleton children from the United Kingdom Millennium Cohort Study. Children were grouped according to breastfeeding duration. Results were stratified by gestational age at birth: 37 to 42 weeks (term, n = 11 101), and 28 to 36 weeks (preterm, n = 778). British Ability Scales tests were administered at age 5 years (naming vocabulary, pattern construction, and picture similarities subscales).

Results The mean scores for all subscales increased with breastfeeding duration. After adjusting for confounders, there was a significant difference in mean score between children who were breastfed and children who were never breastfed: in term children, a two-point increase in score for picture similarities (when breastfed ≥4 months) and naming vocabulary (when breastfed ≥6 months); in preterm children, a 4-point increase for naming vocabulary (when breastfed ≥4 months) and picture similarities (when breastfed ≥2 months) and a 6-point increase for pattern construction (when breastfed ≥2 months). These differences suggest that breastfed children will be 1 to 6 months ahead of children who were never breastfed.

Conclusions In white, singleton children in the United Kingdom, breastfeeding is associated with improved cognitive development, particularly in children born preterm. *(J Pediatr 2012;160:25-32)*.

Children were recruited at approximately age 9 months (sweep 1), and detailed information was collected on a range of socioeconomic and health factors with parental interview. Parents were interviewed again when the children were 3, 5, and 7 years of age (sweeps 2-4).

Infant Feeding. Breastfeeding initiation was assessed by the sweep 1 question, "Did you ever try to breastfeed your baby?" Breastfeeding duration and exclusivity were estimated by using the sweep 1 questions about the age of the infant when last given breast milk and when first given formula, other types of milk, and solid foods. Breastfeeding duration after sweep 1 was assessed by using the sweep 2 question, "How old was the child when s/he last had breast milk?"

Cognitive Development. Cognitive development was assessed at sweep 3 by using the British Ability Scales (BAS)

Statistical Methods

All analysis was conducted separately in children who were born at term (gestation ≥37 completed weeks) and children who were born preterm (gestation 28-36 weeks). The mean BAS score for each subscale was estimated in each breastfeeding group. Linear regression was used to estimate the difference in mean BAS scores across breastfeeding groups after adjustment for baby's sex, birth weight, and gestational age at birth (in weeks), and the following potential confounders and mediators.

A variable was considered statistically significant when any of its co-efficients yielded a Wald test P value <.05. The variables that remained in the partially and fully adjusted final models are given in the footnotes to Tables I

How Do These Differences in BAS Scores Compare with the Progress of an Average 5-Year-Old Child?

The fully adjusted differences from Tables I have been converted into age-equivalent scores that indicate the child's developmental progress; these differences show how many months ahead breastfed children are compared with children who were never breastfed. In the term group, children who were breastfed for at least 4 months tended to be approximately 3 months ahead of children who were never breastfed on picture similarities and children breastfed for at least 6 months were approximately 2 to 3 months ahead on naming vocabulary

Table I. Regression coefficients showing difference in mean BAS scores for breastfed compared with never breastfed children (born at term)

		Any breastfeeding (partial or exclusive)			Exclusive breastfeeding
Duration of breastfeeding	Mean (n)	Crude Coefficient (95% CI)	Partially adjusted coefficient* (95% CI)	Fully adjusted coefficient† (95% CI)	Fully adjusted coefficient† (95% CI)
BAS naming vocabulary scale		n = 10 944	n = 10 929	n = 10 416	n = 10 416
Never	106.5 (3825)	Reference	Reference	Reference	Reference
<2.0 months	110.2 (2901)	3.7 (2.8-4.6)	0.7 (−0.1-1.5)	0.7 (−0.1-1.5)	1.1 (0.4-1.9)
2.0-3.9 months	111.8 (1047)	5.4 (4.1-6.6)	1.2 (0-2.4)	1.2 (0-2.4)	1.0 (0-2.0)
4.0-5.9 months‡	113.0 (889)	6.5 (5.1-7.9)	1.2 (0-2.5)	1.0 (−0.3-2.3)	
6.0-11.9 months	114.1 (1392)	7.7 (6.5-8.8)	2.2 (1.2-3.2)	2.0 (1.0-3.0)	1.6 (0.6-2.5)
≥12.0 months	114.2 (890)	7.7 (6.6-8.9)	2.4 (1.3-3.5)	2.4 (1.3-3.6)	
BAS picture similarities scale		n = 10 957	n = 10 949	n = 10 526	n = 10 641
Never	79.9 (3836)	Reference	Reference	Reference	Reference
<2.0 months	82.4 (2901)	2.5 (1.8-3.2)	1.4 (0.7-2.1)	1.4 (0.7-2.1)	1.4 (0.7-2.0)
2.0-3.9 months	82.6 (1047)	2.7 (1.7-3.7)	1.0 (0.1-1.9)	0.9 (0-1.9)	1.4 (0.6-2.2)
4.0-5.9 months‡	83.8 (889)	4.0 (3.0-5.0)	1.8 (0.9-2.8)	1.7 (0.8-2.7)	
6.0-11.9 months	84.1 (1393)	4.2 (3.2-5.2)	2.0 (1.0-3.0)	1.9 (0.9-2.9)	2.0 (1.1-3.0)
≥12.0 months	83.9 (891)	4.0 (3.0-5.0)	1.7 (0.7-2.7)	1.9 (0.9-2.8)	
BAS pattern construction scale		n = 10 902	n = 10 887	n = 10 678	n = 10 678
Never	85.4 (3812)	Reference	Reference	Reference	Reference
<2.0 months	88.5 (2885)	3.1 (2.0-4.2)	0.9 (−0.2-2.0)	1.0 (−0.1-2.1)	1.1 (0.1-2.1)
2.0-3.9 months	90.4 (1042)	5.0 (3.6-6.4)	1.7 (0.4-3.0)	1.7 (0.3-3.0)	2.1 (0.9-3.4)
4.0-5.9 months‡	92.2 (886)	6.8 (5.2-8.4)	2.5 (1.0-4.0)	2.4 (0.8-3.9)	
6.0-11.9 months	92.1 (1389)	6.7 (5.2-8.2)	2.0 (0.6-3.4)	2.0 (0.5-3.4)	1.4 (0-2.8)
≥12.0 months	91.3 (888)	5.9 (4.3-7.6)	1.1 (−0.5-2.7)	1.0 (−0.6-2.6)	

*All models were adjusted for gestation, birth weight, baby's sex, mother's age (BAS naming vocabulary and BAS picture similarities only), household socioeconomic status, mother's education, whether the baby was firstborn (BAS naming vocabulary and BAS picture similarities only), alcohol in pregnancy (BAS naming vocabulary and BAS pattern construction only), smoking in pregnancy (BAS pattern construction only), admission to neonatal intensive care unit (BAS naming vocabulary and BAS pattern construction only), and language spoken at home (BAS naming vocabulary only).
†All models were adjusted as in * with additional adjustment for BAS naming vocabulary: maternal belief at sweep 1 in the importance of stimulation and regular eating and sleeping patterns; maternal reading with child and getting child to obey instructions at sweep 3; maternal depression at sweep 3; maternal parenting competence at sweep 3; and child care at sweep 1; and whether full/part time at school. BAS picture similarities: getting child to obey instructions at sweep 3; maternal depression at sweep 3; child care at sweep 1; and months since started school. BAS pattern construction: maternal belief at sweep 1 in the importance of talking to a baby and regular eating and sleeping patterns; maternal telling stories to child, painting/drawing with the child and spends plenty of time with child at sweep 3; maternal depression at sweep 3; months since started school; and whether full/part time at school.
‡For exclusive breastfeeding results, this category is ≥4 months.