Antibiotics and the Risk of Breast Cancer

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Background: Two recent studies found a positive association between antibiotic use and the risk of breast cancer.
Methods: Using information from the U.K. General Practice Research Database, we identified 1268 cases of incident breast cancer (40- to 79-year-old women diagnosed in 1987 to 2002 who had at least 6 years of history recorded in the General Practice Research Database) and 6291 female controls matched to the cases on age, general practice, and duration of history recorded in the General Practice Research Database. We ascertained antibiotic prescriptions (penicillins, cephalosporins, sulfonamides, macrolides, tetracyclines, quinolones, metronidazole, and nitrofurantoin) recorded up to 1 year before the index date.
Results: Odds ratios (95% confidence intervals) of breast cancer for 0, 1–50, 51–100, 101–500, and 501 or more cumulative days of antibiotic use were 1.0 (reference), 1.0 (0.9–1.2), 0.9 (0.7–1.2), 0.9 (0.7–1.3), and 1.2 (0.6–2.4).
Conclusions: These data do not support the hypothesis that antibiotic use is associated with an increased risk of breast cancer.

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Several studies have linked antibiotic use to the risk of breast cancer. Knekt et al[1] found an increased risk of breast cancer during 18 years of follow-up among women younger than age 50 years who reported current or past use of antibiotics for urinary tract infections at study entry. Compared with nonusers, the relative risk for women with less than 10 years of follow-up was 1.7 (95% confidence interval [CI] 1.1–2.7), and for those with more than 10 years of follow up, it was 1.9 (1.1–3.4). Velicer et al[2] noted that intestinal microflora have the ability to metabolize phytochemicals from edible plants into compounds that may protect against cancer, and a reduced concentration of these compounds in the intestinal lumen as a result of antibiotic use might increase the risk of breast cancer or other types of cancer. These investigators also postulated that antibiotic use might increase or decrease the risk of breast cancer through effects on immune or inflammatory mediators or the metabolism of estrogens. Recently, using data from Group Health Cooperative of Puget Sound, Velicer et al[3] reported an increased risk of breast cancer among women who used antibiotics during a median 16 to 20 years of follow-up. Compared with nonusers, relative risk estimates were greater than 2 for women in the highest categories of cumulative use (501–1000 days and >1000 days) and approximately 1.5 in the lowest category (1–50 days). This study found increased relative risks of breast cancer in relation to 6 of the 8 classes of antibiotics analyzed.

To further investigate the relation between antibiotic use and breast cancer, we undertook a case–control study using information from the U.K. General Practice Research Database.

METHODS

Data Resource

We used computerized medical record information from 270 general practices in the United Kingdom that contribute data to the General Practice Research Database and have agreed to provide additional documents such as hospital discharge summaries and consultants' letters when requested. General practitioners enter demographic and diagnostic data, and they use the computer software to generate prescriptions, thereby ensuring a complete record of prescribed medications. We have validated this database and confirmed its suitability for studies of the incidence and etiology of breast cancer.[4–8]

The study protocol was approved by the Scientific and Ethical Advisory Group of the General Practice Research Database.

Base Population

The base population comprised 574,812 women who were 40 to 79 years old during 1987 to 2002. Women were eligible from the start of their follow-up in the General Practice Research Database until they developed breast cancer, transferred from their general practice, or died.

Cases

Cases were women in the base population who had incident breast cancer and at least 6 years of recorded history before their index (diagnosis) date. Among a random sample of 100 cases, treatments consistent with a diagnosis of breast cancer were recorded for 98 cases.

Controls

For each case, we matched up to 5 female controls by age (within 2 years), general practice, and duration of history recorded in the General Practice Research Database before the index date of the case to which they were matched (within 1 year).

Antibiotic Use

We assessed prescriptions for 8 classes of antibiotics (penicillins, cephalosporins, sulfonamides, macrolides, tetracyclines, quinolones, metronidazole, and nitrofurantoin) recorded before 1 year before the index date ("exposure reference date"). We consider antibiotics prescribed within 1 year before a diagnosis of breast cancer unlikely to be etiologically relevant. By design, all cases and controls had at least 5 years of recorded history in the General Practice Research Database before their exposure reference date. From the number of pills prescribed and the instructions for use, we could determine the cumulative days of intended use for more than 90% of prescriptions. When we could not determine duration of use for a prescription, we imputed a value of 7 days. We estimated relative risks for categories of cumulative duration of antibiotic use in relation to no use (represented by women with no recorded prescriptions). Separately, we also analyzed the number of antibiotic prescriptions recorded without regard to their intended duration of use.

Other Covariates

We evaluated as potential confounders body mass index (BMI), use of hormone replacement therapy, history of benign proliferative breast disease, frequency of mammograms, and frequency of visits to the general practice. All covariates were assessed in relation to the same exposure reference date as for antibiotic prescriptions.

Statistical Methods

We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between cumulative days of antibiotics and the risk of breast cancer.

RESULTS

We identified 1268 cases of incident breast cancer among women age 40 to 79 years and matched them to 6291 controls. The median duration of recorded history before the index date was 94 months (maximum 154 months). Characteristics of the cases and controls are listed in Table 1. High body mass index, use of hormone replacement therapy, history of benign proliferative breast disease, frequency of mammograms, and frequency of visits to general practice were independently associated with an increased risk of breast cancer.

Conditional on the matching factors, risk estimates for various categories of days of antibiotic use in relation to no antibiotic use are presented in Table 2. All estimates were close to 1.0. Separately, in an analysis of the number of antibiotic prescriptions recorded (0, 1–10, 11–25, 26–50, and 51 or more), we similarly found no evidence for an association between antibiotic use and the risk of breast cancer.

Adjusting for potential confounders (BMI, use of hormone replacement therapy, history of benign proliferative breast disease, frequency of mammograms, and frequency of visits to general practice) produced no material change in the risk estimate for any category of cumulative antibiotic use.

Risk estimates for specific antibiotic classes were either similar to the overall results or not estimable because of small numbers. Data for the 4 most commonly used classes are listed in Table 2. The risk of breast cancer was highest for macrolide use for 101–500 days (OR = 6.3; 95% CI = 2.5–15.9), but this estimate is based on only 10 cases and 8 controls. Fewer than 10% of study subjects had any recorded use of sulfonamides, quinolones, metronidazole, or nitrofurantoin.

TABLE 1. Characteristics of Cases and Controls

Characteristic	Cases (n = 1268) %	Controls (n = 6291) %
Age (years)		
40–49	19	19
50–59	31	31
60–69	27	28
70–79	22	22
Body mass index (kg/m^2)		
<24	28	27
24–28	23	23
>28	22	21
Unknown	27	30
Hormone replacement therapy		
None recorded	76	82
Past*	9	7
Recent*	15	11
History of benign proliferative breast disease		
None	96	98
Any	4	2
No. of mammograms per year		
0	64	66
>0 to 0.2	17	16
>0.2	19	18
No. of visits to general practice per year		
0	1	2
>0 to 3	36	39
>3	64	60

*One or more hormone replacement therapy prescriptions recorded during the year before the exposure reference date is defined as recent use; any earlier prescription is defined as past use.

DISCUSSION

The case–control study of Velicer et al,[3] which found an increased risk of breast cancer associated with exposure to several commonly used classes of antibiotics, created renewed interest in the hypothesis that various antibiotics might alter women's risk of developing breast cancer.[2] The only previously published epidemiologic study on this topic[1] did not provide persuasive evidence of an increase in the risk of breast cancer in relation to antibiotic use because the study

TABLE 2. Cumulative Days of Antibiotic Use and Risk of Breast Cancer

	Cases (n = 1268)		Controls (n = 6291)		
	No.	(%)	No.	(%)	OR (95% CI)
All antibiotics					
0*	343	27	1,700	27	1.0
1–50	747	59	3,660	58	1.0 (0.9–1.2)
51–100	106	8	568	9	0.9 (0.7–1.2)
101–500	61	5	319	5	0.9 (0.7–1.3)
501+	11	1	44	1	1.2 (0.6–2.4)
Penicillins					
0*	495	39	2,547	40	1.0
1–50	705	56	3,417	54	1.1 (0.9–1.2)
51–100	51	4	250	4	1.1 (0.8–1.5)
101–500	15	1	72	1	1.1 (0.6–1.9)
501+	2	<1	5	<1	2.1 (0.4–10.8)
Tetracyclines					
0*	985	78	4,831	77	1.0
1–50	248	20	1,325	21	0.9 (0.8–1.1)
51–100	16	1	63	1	1.2 (0.7–2.1)
101–500	12	1	46	1	1.3 (0.7–2.4)
501+	7	1	26	<1	1.3 (0.6–3.1)
Macrolides					
0*	1,023	81	5,113	81	1.0
1–50	228	18	1,138	18	1.0 (0.9–1.1)
51–100	7	1	31	1	1.1 (0.5–2.5)
101–500	10	1	8	<1	6.3 (2.5–15.9)
501+	0	<1	1	<1	0
Cephalosporins					
0*	1,044	82	5,117	81	1.0
1–50	211	17	1,117	18	0.9 (0.8–1.1)
51–100	9	1	33	1	1.3 (0.6–2.8)
101–500	4	<1	22	<1	0.9 (0.3–2.6)
501+	0	<1	2	<1	0

*Reference category.

evaluated only self-reported current or past use of antibiotics to treat urinary tract infections at one point in time (the start of 18 years of follow up). There are notable aspects of the study by Velicer et al.[3] First, an increase in risk of breast cancer was observed for 6 of the 8 antibiotic classes evaluated. Second, the increased risk was observed for both premenopausal and postmenopausal women. Third, there was an increased risk of breast cancer even in the lowest exposure category of 1–50 days of use (OR = 1.45; 95% CI = 1.24–1.69).

The data we have presented do not support the hypothesis that antibiotic use is associated with an increased risk of breast cancer. A limitation of our study is that the median duration of follow up (94 months) is shorter than in previous observational studies.[1,3] We also did not have information on several hormonal risk factors for breast cancer such as age at menarche, age at first live birth, or parity. However, these factors did not confound the association between antibiotic use and breast cancer in the study of Velicer et al.[3] Because we know of no reason why these factors should be associated with antibiotic use in our study population, we consider it unlikely that our results are confounded by these factors. Velicer and colleagues excluded noninvasive breast cancers from their study. Although we cannot routinely distinguish noninvasive from invasive breast cancers in the General Practice Research Database, noninvasive lesions account for a minority of breast cancers in the United Kingdom as in the United States, and we think that the inclusion of cases with noninvasive breast cancer is unlikely to have materially influenced our results. The data resource we used is a major strength of our study; extensive work done by our group on the General Practice Research Database has repeatedly demonstrated its validity and completeness for pharmacoepidemiologic investigations, including studies of cancer.[4–8]

In summary, current data from the General Practice Research Database do not provide evidence in support of the hypothesis that several classes of commonly used antibiotics increase the risk of breast cancer.

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Anthropometric Characteristics and Risk of Multiple Myeloma

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Background: Few studies have examined obesity and risk for multiple myeloma, and the results are inconsistent. Laboratory evidence suggests mechanisms through which obesity could influence carcinogenesis of this hematopoietic malignancy.

Methods: We examined the association between anthropometric characteristics and incident multiple myeloma in a prospective, population-based sample of 37,083 postmenopausal women. In 1986, the women completed a mailed questionnaire that included self-report of height and weight, and friend measurement of waist and hip circumferences. During 16 years of follow up, 95 cases of multiple myeloma were identified through linkage to the Iowa Cancer Registry.

Results: In an age-adjusted model, women in the highest category of several anthropometric measurements compared with the lowest category were at increased risk of developing multiple myeloma. For body mass index (kg/m^2), the rate ratio (95% confidence interval) was 1.5 (0.92–2.6); for weight, 1.9 (1.1–3.4); for waist circumference, 2.0 (1.1–3.5); and for hip circumference, 1.8 (1.0–3.0).

Conclusion: Greater adiposity may increase the risk of multiple myeloma.

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Two case–control studies and 3 cohort studies have examined obesity and incident multiple myeloma with inconsistent results—possibly due to a small number of multiple myeloma cases, the choice of exposure measurements, or the cut points that define the measurements.[1–5] One mechanism by which excess adiposity may increase the risk of multiple myeloma is through the cytokine interleukin-6 (IL-6), which is involved in proliferation and survival of plasma cells.[6] Studies have shown this cytokine is also synthesized in and secreted from adipose tissue, and may act as a circulating hormone.[7] Furthermore, insulin-like growth factor I (IGF-I), which is associated with obesity, has been found to stimulate proliferation and inhibit apoptosis in myeloma cells.[8,9] The objective of this study was to help clarify the relation between obesity and multiple myeloma by examining the association between several anthropometric characteristics and incident multiple myeloma in a prospective, population-based study of postmenopausal women.

METHODS

Study Subjects

In 1986, the Iowa Women's Health Study was initiated to examine risk factors associated with cancer in a population-based cohort. A total of 41,836 women, age 55 to 69 years, completed the baseline questionnaire (43% response rate). The questionnaire included anthropometric data, diet, reproductive and medical history, and other possible risk factors for cancer. Subjects provided informed consent under a protocol approved for human subjects' research by the University of Minnesota Institutional Review Board.

To assess anthropometric characteristics, the study participants received a tape measure with the questionnaire and instructions for taking specified measurements. It was suggested that a friend or relative assist with the measurements to improve accuracy. Waist circumference was measured 1 inch above the umbilicus and hip circumference was measured at the level of maximal circumference. We calculated body mass index (BMI; kg/m^2) from the self-reported height and weight measurements. Self-reported and self-measured variables in this cohort have been shown to be both reliable and valid.[10] We combined information on frequency and intensity of leisure-time exercise to create a 3-level activity score (low, moderate, high).

Cohort Follow Up

Vital status was assessed through mailed follow-up questionnaires, by linkage to the State of Iowa death certificates, and by linkage to the National Death Index. We estimate that 99% of deaths have been identified.

Incident multiple myeloma cases through December 2001 were ascertained through linkage to the State Health Registry of Iowa, which participates in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Because the migration rate from Iowa was less than 1% annually within this cohort, nearly complete follow up for cancer incidence was obtained. A total of 95 incident multiple myeloma cases were identified among the eligible cohort members using topographic and morphologic data from the International Classification of Diseases for Oncology (third edition).[11]

Data Analysis

Women were excluded at baseline if they reported cancer other than skin cancer (n = 3830), were premenopausal (n = 547), or were classified as underweight (BMI $<$18.5 kg/m^2; n = 379), resulting in a total of 37,083 women who were observed from 1986 through 2001. We excluded underweight women from analyses because our goal was to compare overweight and obese women to normal-weight women, and we did not want very thin women in the reference group.

Characteristics assessed at baseline were examined to determine if they differed according to multiple myeloma status. We analyzed associations between anthropometric characteristics and multiple myeloma using Cox proportional hazards regression. Risk factors identified by previous studies of multiple myeloma as well as variables associated with adiposity were examined as potential confounders. Because none of the potential confounding variables altered the rate ratios by 10% or more, the risk of multiple myeloma was calculated from age-adjusted rate ratios (RRs) and 95% confidence intervals (CIs). We performed a linear test for trend by creating a variable representing the median value of each category of the covariate of interest and including this variable as a continuous term in the regression model, which was evaluated by a Wald chi-squared test.

RESULTS

After a maximum of 16 years of follow up of the cohort (mean ± standard deviation: 14.3 ± 3.6), there were 95 incident cases of multiple myeloma. At the time of diagnosis, 12% of cases were 55 to 64 years of age, 44% were 65 to 74, and 44% were 75 to 84. The rate of incident multiple myeloma in our study cohort was 17.9 per 100,000 person-years of follow up. In comparison, the incidence rates for 1990 to 2001 for white women, 50 years of age and older, were 15.4 per 100,000 persons in Iowa and 14.4 per 100,000 persons in the United States.[12] Women diagnosed with incident multiple myeloma were older at baseline compared with noncases (Table 1). Education, BMI, physical activity, diabetes, total calories consumed, alcohol consumption, smoking, and hormone replacement therapy were distributed similarly among multiple myeloma cases and noncases.

The age-adjusted rate ratios of incident multiple myeloma in relation to anthropometric characteristics are presented in Table 2. There was an increased risk of multiple myeloma for women with greater adiposity as measured by BMI, weight, waist/hip ratio, and waist and hip circumferences. Women in the highest category had a 1.5- to 2-fold increased risk compared with women in the lowest category. These results were unaffected by adjustment for other putative multiple myeloma risk factors. These associations were virtually unchanged after exclusion of cases diagnosed during the first 2 years of follow up.

DISCUSSION

We found a greater risk of developing multiple myeloma associated with greater adiposity as measured by weight, BMI, and waist and hip circumferences. This result is consistent with findings from studies that include a larger number of cases.[2,3,5] Brown et al[5] reported an increased risk of incident multiple myeloma among persons who were overweight (BMI >25 kg/m^2, OR = 1.5; 95% CI = 1.1–2.0) and obese (BMI >30 kg/m^2, 1.9; 1.2–3.1) versus normal-

TABLE 1. Baseline Characteristics According to Incident Multiple Myeloma Status

	Incident Multiple Myeloma	
	Yes (n = 95) %	No (n = 36,988) %
Age at baseline (years)		
55–59	20	35
60–64	37	35
65–69	43	29
Body mass index (kg/m^2)*		
Normal	32	39
Overweight	39	37
Obese	29	24
Education		
<High school	20	20
High school	44	42
>High school	36	39
Residence		
Farm or rural area	28	27
City, population ≤10,000	38	39
City, population >10,000	34	34
Cigarette smoking		
Never	67	66
Past	22	19
Current	11	15
Smoking (pack-years)		
None	69	67
1–19	11	14
20–39	11	11
40+	9	9
Alcohol (g/d)		
None	56	57
<5	31	25
≥5	14	19
Regular physical activity		
No	63	58
Yes	37	42
Physical activity level		
Low	45	47
Moderate	34	28
High	21	25
Estrogen use		
Never	64	62
Current	7	11
Past	29	27
Diabetes history		
No	91	94
Yes	9	6
Energy intake tertiles (kcal/d)		
Low	33	33
Middle	41	33
High	26	33

*WHO BMI categories: normal = 18.5–24.9 kg/m^2, overweight = 25.0–29.9 kg/m^2, obese = ≥30 kg/m^2.

TABLE 2. Associations of Anthropometric Variables With Multiple Myeloma in Postmenopausal Women

	No. of Cases	Person-Years	Rate per 100,000 Person-Years	Age-Adjusted RR (95% CI)
BMI*				
Normal weight†	30	205,751	14.6	1.0
Overweight	37	199,279	18.6	1.3 (0.78–2.0)
Obese	28	124,879	22.4	1.5 (0.92–2.6)
P for trend				0.10
Weight tertiles in pounds				
≤137†	19	172,737	11.0	1.0
138–160	40	184,616	21.7	2.0 (1.1–3.4)
≥161	36	172,556	20.9	1.9 (1.1–3.4)
P for trend				0.04
Height tertiles in inches				
≤62†	26	142,727	18.2	1.0
63–65	39	234,170	16.7	0.9 (0.57–1.5)
≥66	30	153,012	19.6	1.2 (0.68–2.0)
P for trend				0.52
Waist/hip ratio tertiles				
≤0.79†	24	175,850	13.6	1.0
0.80–0.87	36	188,449	19.1	1.3 (0.78–2.2)
≥0.88	35	163,369	21.4	1.4 (0.84–2.4)
P for trend				0.20
Waist tertiles in inches				
≤31.75†	19	178,340	10.7	1.0
31.76–36.25	37	176,042	21.0	1.9 (1.1–3.2)
≥36.26	39	173,601	22.5	2.0 (1.1–3.5)
P for trend				0.02
Hip tertiles in inches				
≤39.00†	22	177,235	12.4	1.0
39.01–42.25	35	177,207	19.8	1.6 (0.92–2.7)
≥42.26	38	173,347	21.9	1.8 (1.0–3.0)
P for trend				0.04

Models adjusted for age (continuous). *P* for trend: median value of each category modeled as a continuous variable.

*WHO BMI categories: normal = 18.5–24.9 kg/m^2, overweight = 25.0–29.9 kg/m^2, obese = ≥30 kg/m^2.

†Reference category.

weight white men and women. Similarly, in a large Canadian study, the risk for multiple myeloma was increased for overweight men (1.64; 1.09–2.47) and obese men (2.16; 1.25–3.75) and women (1.92; 1.23–3.00) compared with their normal-weight counterparts.[2] Somewhat elevated odds ratios also were reported for obese versus nonobese white (1.22; 1.05–1.40) and black (1.26; 1.02–1.56) male U.S. veterans.[3] In contrast, 2 cohort studies found no association between either greater BMI[4] or obesity[1] and incident multiple myeloma in women. In both cohort studies, the BMI categories used and the small number of multiple myeloma cases potentially limited the possibility of detecting an association. Friedman et al[4] (with 49 white and 18 black multiple myeloma cases) analyzed a cut point for the highest BMI quartile of 25.78 kg/m^2, which includes both overweight and obese individuals. Similarly, the study by Wolk et al[1] had only 16 women who developed multiple myeloma, and the cut points for overweight and obesity were BMI >23.8 and 28.6 kg/m^2, respectively.

Little is known regarding biologic mechanisms that could explain a link between excess adiposity and increased risk of multiple myeloma. Numerous studies have shown

IL-6 to be involved in the proliferation and differentiation of both normal and malignant plasma cells.[6] This cytokine may increase survival of myeloma cells through inhibition of apoptosis.[6] Although IL-6 is produced in the bone marrow microenvironment, it is also synthesized in adipose tissue.[7] In addition to having autocrine and paracrine effects, IL-6 can also exert hormonal-like effects such as stimulation of the hypothalamic–pituitary–adrenal axis.[7,13] Evidence also suggests that obesity, especially excess abdominal fat, can lead to insulin resistance, which in turn can lead to increased levels of bioavailable insulin and insulin-like growth factors (IGFs). IGF-I is one of many growth factors involved in the hematopoietic process for both normal and malignant cells.[14] Evidence suggests IGF-I stimulates myeloma cell proliferation and inhibits apoptosis[8] independent of IL-6.[9] Recently, it was discovered that IGF-I acts as a chemotactic factor by inducing migration of myeloma cells to the bone marrow in early-stage disease as well as metastasis during late-stage disease.[15]

Several limitations to our study should be considered. Despite a 16-year follow up of over 37,000 women, only 95 incident cases of multiple myeloma were ascertained, thus resulting in some imprecision of the risk estimates. However, the prospective design eliminated the potential for differential recall bias in exposure assessment. Although we had several anthropometric measures with which to assess adiposity, these measures were self-reported or taken by a friend. Self-report or friend measurement, however, has been shown to be reasonably accurate.[10,16] We were unable to assess confounding by immunologic disorders, although these have not been shown consistently to be associated with risk of multiple myeloma. Our study population included only women, most of whom were white; thus, our results may not be generalizable to men or to other ethnic groups.

The results of our study provide support for an increased risk of multiple myeloma among older women with greater adiposity using measures of weight, and waist and hip circumferences. A recent study found a higher BMI among individuals with the variant allele in a polymorphism in the IL-6 gene promoter.[17,18] Investigating this and other gene polymorphisms could shed light on the biologic mechanisms involved in the link between excess adiposity and multiple myeloma carcinogenesis.

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Accuracy of Men's Recall of Their Partner's Time to Pregnancy

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Background: Occupational studies of fertility often rely on men's report of time to pregnancy (TTP). We assessed accuracy of men's report of TTP compared with TTP derived from data from their female partners.

Methods: Men from the Dieckmann diethylstilbestrol cohort were interviewed to assess fertility. Men were asked TTP for their most recent pregnancies. Their female partner was subsequently interviewed separately; TTP derived from her data was used as the gold standard. Our analysis was based on 202 couples.

Results: Men's report was identical to the women's-derived TTP in 32% of couples; 74% differed by no more than 2 cycles. Men tended to underestimate TTP (mean difference = −1.2 cycles). Weighted kappa was 0.5 overall and varied by the man's education, the number of pregnancies he had fathered, his stated confidence in reporting, his exposure to diethylstilbestrol, pregnancy planning, and whether he was still married to the index partner.

Conclusions: Overall accuracy of men's report of TTP was reasonably good, particularly for men who had fathered only one pregnancy.

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Couples who are more fertile will, on average, achieve pregnancy within fewer menstrual cycles. Data on time to pregnancy (TTP) better represents the continuous nature of fertility than does a dichotomous measure such as fertile and infertile. TTP reported by men often is used in occupation-based studies to determine the effects of occupational exposures on fertility.[1–3] In many cases, women are not included in the study because of the sex composition of the occupation, constraints in study design that limit contact with the female partner, or the tendency of women to give birth and then leave the workforce, making them harder to identify and enroll.[1,4]

Despite the wide use of male-reported TTP, the accuracy of men's report has not been determined adequately.[5,6] With the exception of one small study,[7] the validation of men's report has been indirect, based on comparing the frequency distribution of men's reported TTP with expected distributions based on prospective studies or distributions from retrospective data from women.[5] Although such observations suggest that men's reporting may be adequate, these data do not provide a direct test of accuracy. Our objective was to determine the accuracy of men's reported TTP for the most recent pregnancy. We defined accuracy as the man's ability to report TTP compared with data derived from his partner for the same pregnancy.

METHODS

Participants were the sons of women who had enrolled in a double-blind, placebo-controlled study of the effects of diethylstilbestrol (DES) in pregnancy, conducted at the University of Chicago between 1950 and 1952.[8,9] As the detrimental effects of DES on prenatally exposed adults surfaced, the University of Chicago followed all traceable offspring from the study.

Structured telephone interviews with 494 adult sons of women enrolled in the original DES cohort were conducted in 1991.[9] For the most recent pregnancy, regardless of its outcome, men who reported that the couple was not using birth control around the time of conception were asked: "How many months did it take you and your partner to get pregnant with that pregnancy?" Men replying, "Don't know," were asked to give their best guess.

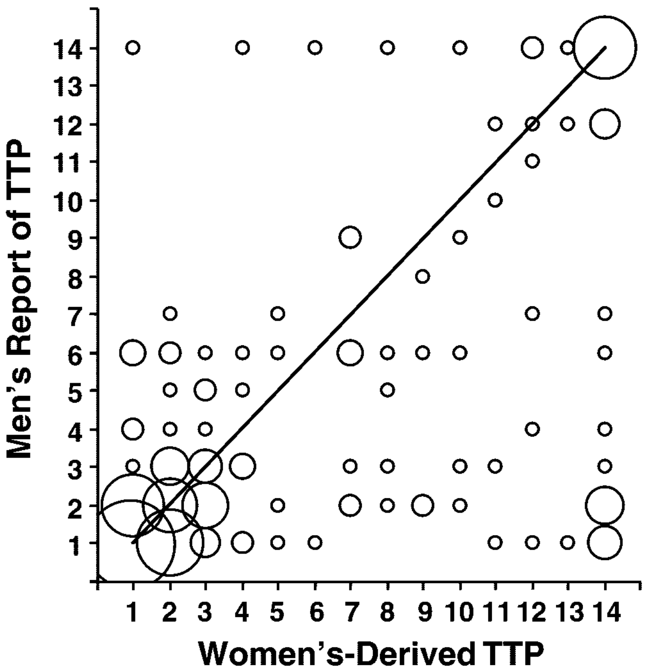

FIGURE 1. Scattergram of male-reported TTP and TTP derived from questioning the female partners (n = 202 couples). Each circle indicates the data pair, with size of circle representing the relative number of individuals in each data pair. The diagonal line represents perfect agreement for each of the points. Thirty couples are concordant at cycle 1, and 16 couples are concordant for ≥14 cycles.

Men's partners were subsequently contacted for an individual telephone interview, which included questions from which TTP for the reference pregnancy was derived. If the reference pregnancy was a first pregnancy or if it was conceived after stopping contraception, the women were asked how many months it took to get pregnant. If the women had had a previous pregnancy and no contraception had been used between pregnancies, TTP was estimated through questions about when menses and sexual intercourse resumed after the prior pregnancy, and whether there were subsequent months without intercourse. Further information was collected about their menstrual cycles to convert the number of months into cycles to conception. Questionnaires for both the men and women are available at http://dir.niehs.nih.gov/direb/home.htm.

Men were excluded from analyses if they never fathered a pregnancy (n = 122), if they did not provide contact information for their partner (n = 38), if the partner could not be contacted or traced (n = 22) or refused participation (n = 7), if the men and women did not report the same pregnancy as being the most recent

TABLE 1. Variation in Weighted Kappa Statistics (Degree of Agreement Between Male-Reported TTP And TTP Derived From Questioning the Female Partners) According to Characteristics of the Men at the Time of Interview

	No. (%)	Kappa Statistic (95% CI)
Overall	202 (100)	0.50 (0.40–0.60)
Men's education		
High school or less	17 (8)	0.30 (0.00–0.61)
Some college	53 (26)	0.47 (0.27–0.67)
College graduate	59 (29)	0.51 (0.33–0.69)
Graduate school	73 (36)	0.55 (0.40–0.71)
Family income (n = 198)		
<$30,000	19 (9)	0.46 (0.15–0.76)
$30,000–44,999	41 (21)	0.47 (0.24–0.71)
$45,000+	138 (70)	0.53 (0.41–0.65)
No. pregnancies		
1	35 (17)	0.73 (0.48–0.99)
>1	167 (83)	0.45 (0.34–0.56)
Time since pregnancy (yrs)		
0–4.9	83 (41)	0.47 (0.32–0.63)
5.0–9.9	81 (40)	0.55 (0.39–0.71)
≥10.0	38 (19)	0.42 (0.21–0.63)
Confidence in TTP		
Guessed	21 (10)	0.43 (0.13–0.74)
Answered without having to guess	181 (90)	0.50 (0.40–0.61)
Male exposed to DES		
Exposed	106 (53)	0.59 (0.45–0.73)
Unexposed	96 (47)	0.41 (0.27–0.55)
Pregnancy planning		
Reported "trying"	148 (73)	0.56 (0.44–0.67)
Did not report "trying"	54 (27)	0.36 (0.17–0.56)
Still married to partner		
Yes	187 (93)	0.51 (0.40–0.61)
No	15 (7)	0.31 (0.01–0.61)

(n = 8), if either partner (19 men, 34 women) or both partners (n = 40) reported using birth control around the time of conception, or if TTP data were missing for either partner (n = 2). After exclusions, there were 202 couples available for analysis. This sample included 106 men exposed prenatally to DES and 96 unexposed. Exposed and unexposed groups were combined in analysis because DES exposure was not related to fertility.[9]

Statistical Analyses

TTP derived from the woman's report was considered the gold standard; it was assessed in units of cycles. The data on number of months reported by the men was taken to mean number of cycles. Because infertility treatment often begins after a year of trying to conceive, TTP typically is censored in analysis at greater than 1 year (ie, longer than 13 cycles).[10] We grouped our data similarly, treating TTP of 14 or more cycles as a single category. Weighted kappa statistics were calculated to quantify agreement between the men's report and women's-derived TTP. Kappa statistics were weighted to allow for partial agreement based on how closely the men's report matched the women's-derived TTP. (Details regarding the calculation of kappa are provided in an appendix, available with the electronic version of this article.)

TABLE 2. Difference in Male-Reported TTP and TTP Derived From Data Collected From Female Partners (Men's-Reported Minus Women's-Derived TTP, in Cycles)

TTP Derived From Women	No.	Mean Difference ± SD
Overall	202	−1.2 ± 4.1
Categories		
1–3	117	0.4 ± 1.9
4–6	14	0.2 ± 4.3
7–11	26	−2.9 ± 3.9
≥12	45	−4.7 ± 5.7

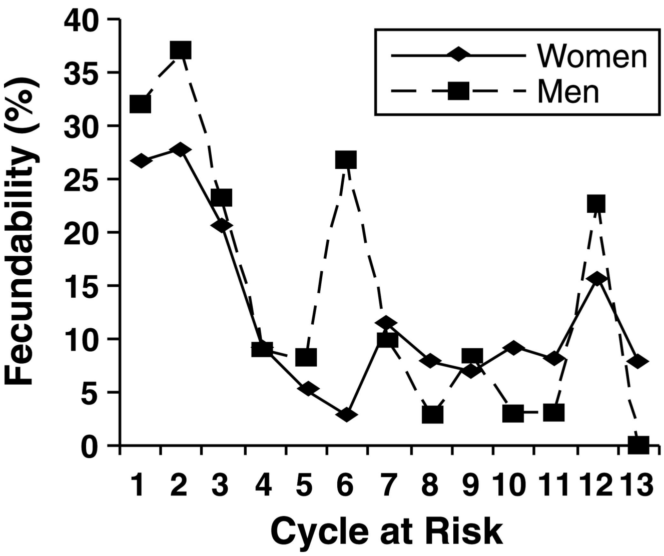

FIGURE 2. Fecundability in each cycle at risk stratified by source of TTP data.

RESULTS

Ninety-six percent of participants were white, and 92% had more than a high school education. The women were demographically very similar to the men but somewhat less educated (22% with high school or less).

The men's-reported TTP was identical to the women's-derived TTP in 32% of couples, whereas 74% differed by no more than 2 cycles (Fig. 1). We examined the difference in the men's reports versus the women's derived TTP by subtracting the women's estimate from the men's. On average, men underestimated the TTP (mean difference = −1.2 cycles) cycles (Table 2). When the women's-derived TTP was 6 months or less, average differences between the men's report and the women's-derived TTP were small. However, when the women's-derived TTP was more than 6 months, men often underestimated TTP by several cycles (Table 2).

Figure 2 depicts cycle-specific conception rates as reported by men and derived from their partners. The conception rate at cycle 1, which estimates the mean fecundability of the group, was 32% by the men's report and 27% for the women's-derived data. Although the general conception rate declines as expected in later cycles for both the men's and women's data, we found marked increases for men at 6 and 12 months, indicating digit preference.

The overall Pearson's correlation between men's-reported TTP and women's-derived TTP was 0.62, with a weighted kappa statistic of 0.50. Table 1 lists the weighted kappa statistics for specific categories of men. Weighted kappa values tended to vary by the man's education, number of prior pregnancies he fathered, his confidence in reporting, his DES exposure status, pregnancy planning, and whether or not he was still married to the index partner.

DISCUSSION

TTP cannot be validated easily. It is not recorded in medical records unless the attempt is particularly long and couples seek medical treatment of infertility. In this study, we used data from women as the gold standard for assessing men's reporting accuracy. We asked female partners a series of detailed questions (including menstrual cycle length, when they stopped contraception to conceive, periods of sexual abstinence, and postpartum amenorrhea for women who had not used birth control after a prior pregnancy) to derive as valid a self-report measure as possible.

Few studies have assessed men's ability to report TTP. One study of 56 couples found that TTP reports given by men were highly correlated with TTP from their partners (r = 0.84).[7] Indirect comparisons found that the distributions of TTP reported by men were similar to distributions from prospectively collected data or to distributions for women's-reported TTP.[5,11,12]

In our sample of mostly married couples with planned pregnancies, we found that the overall accuracy of men's report of TTP was reasonably good. On average, men underestimated TTP by about one cycle, primarily because of substantial underestimation of some of the long TTPs. We also found that encouraging men to give their best estimate of TTP after they said they didn't know, is able to yield valuable data. Men who were reporting on their only pregnancy tended to report very accurately. However, we could not investigate whether this occurs with only one pregnancy or with only first pregnancies because we collected TTP only for the most recent pregnancy.

Men in our sample with no education beyond high school tended to report poorly, although our numbers in that group were small. This finding could be a concern in occupational studies of fertility where certain groups of workers (eg, the most highly exposed) have limited education.

Our finding that DES-exposed men tended to report more accurately is of interest. DES-exposed men did not have reduced fertility,[9] but they may have more knowledge or concern about their reproductive health, resulting in better reporting.

Recall time in this study (ie, time since most recent pregnancy) ranged from very short (26 men had currently pregnant partners or the child was born within a year of the interview) to more than 18 years, with 38 (19%) of the pregnancies ending more than 10 years before interview. Despite this wide variation, we found no evidence that the men's reporting accuracy varied substantially with time since the pregnancy. This has also been found for accuracy of women's report.[13]

In summary, men's report of TTP appears to be reasonably good. However, we excluded 53 couples (11% of the original sample) who disagreed about whether they had used birth control around time of conception. This excludes men who would potentially report less accurately. In addition, further study of men who have limited education is needed. If this group's low reporting accuracy is confirmed, more complicated study designs incorporating partners or prospective monitoring of TTP will be required to assess their fertility.

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Maternal Smoking, Genetic Variation of Glutathione *S*-Transferases, and Risk for Orofacial Clefts

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Background: Maternal smoking is a known risk factor for orofacial clefts. We investigated whether risk is greater among offspring who lack the genetic capacity to produce glutathione *S*-transferase enzymes relevant to detoxification of chemicals in cigarette smoke.
Methods: Using a population-based case–control design, we genotyped 423 California infants with an isolated cleft and 294 nonmalformed controls for null variants of the glutathione *S*-transferases *GSTT1* and *GSTM1*.
Results: If a mother smoked during pregnancy and her fetus was homozygous null for *GSTT1*, the risk of isolated cleft lip with or without cleft palate was tripled (odds ratio = 2.9; 95% confidence interval = 1.2–7.2). For fetuses who were homozygous null for *GSTM1* and whose mothers smoked ≥20 cigarettes per day, we found nearly a 7-fold increased risk (6.8; 0.82–57). Combined absence of *GSTM1* and *GSTT1* enzymes among the offspring of smoking mothers was associated with a nearly 6-fold increased risk for cleft lip (6.3; 1.3–42). A similar increased risk for cleft palate was associated with absence of *GSTM1*, but not for absence of *GSTT1*.
Conclusions: Maternal smoking during pregnancy increases risks for clefts among fetuses lacking enzymes involved in the detoxification of tobacco-derived chemicals.

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Oral clefts have been associated with smoking during pregnancy.[1–11] The risk to an embryo is presumably related to number of cigarettes smoked, as well as materno-placental transfer and detoxification. Glutathione *S*-transferases (GSTs) are important phase II detoxification enzymes, conjugating activated reactive intermediates to make them more water-soluble so that they can be excreted. *GSTM1* detoxifies active metabolites of polycyclic aromatic hydrocarbons, whereas *GSTT1* catalyzes the *S*-glutathionation of low-molecular-weight halogenated compounds and reactive epoxides.[12–14] GSTs are expressed in embryonic tissues, suggesting detoxification in utero is important.[15] We hypothesized that a lack of *GSTT1* or *GSTM1* activity would decrease the biotransformation of teratogenic intermediates originating from maternal tobacco smoking during pregnancy, thus increasing infant susceptibility to orofacial clefts.

METHODS

This research was approved by the California State Committee for the Protection of Human Subjects and Children's Hospital and Research Center Oakland Institutional Review Boards.

Study Population

Details of the population-based case–control study used for these analyses have been described elsewhere.[2] Preliminary results of genotyping of *GSTM1* from a subset of these cases were previously published.[17] Case infants or fetuses with an isolated orofacial cleft (cleft lip with or without palate; or cleft palate) were ascertained by reviewing medical records at all hospitals and genetic centers in a known geographic population base. Eligible were infants (within 1 year of birth) and fetuses diagnosed with an orofacial cleft among the cohort of 552,601 births and fetal deaths that occurred between 1 January 1987 and 31 December 1989 to women residing in most counties in California (metropolitan areas of Los Angeles and San Francisco were excluded). Infants diagnosed with any chromosomal aneusomy were excluded (n = 81). Nonmalformed controls (n = 972), delivered of mothers residing in the same counties as cases, were electronically selected from California vital records using a pseudorandom number.

Questionnaire

We interviewed mothers of cases and controls in English (91%) or Spanish, nearly all by telephone. We excluded women who only spoke languages other than English or Spanish (26 cases and 33 controls) and 3 case mothers who died before interview contact, yielding 863 cases and 939 controls eligible. Interviews were completed an average of 3.5 years after delivery for cases and 3.6 years after delivery for controls. To assess active maternal smoking exposures, women were asked how many cigarettes they smoked daily for the 4-month period beginning 1 month before conception and including the 3 months after conception, as well as for each month during the period. To assess passive smoke exposures in the 4-month period, a woman was asked whether anyone smoked inside her home (including specific questions about paternal smoking), near her at work or school, or while she was commuting to work or school, and whether she regularly frequented (at least once a week) a place such as a restaurant or laundromat where others smoked nearby.

Genotyping

A DNA specimen (residual dried blood spots from newborn screening) was identified for 83% of cases and 87% of controls. To minimize the number of samples to be genotyped, the 652 control samples were randomly reduced to 299. Genotyping methods for null polymorphisms of *GSTM1* and *GSTT1* were adapted from Arand et al[18] and are available with the electronic version of this article.

Statistical Analyses

Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to estimate risks.

RESULTS

Maternal and infant characteristics of cases (n = 437) and controls (n = 299) are available elsewhere.[19] We genotyped 97% (n = 423) of cases and 98% (n = 294) of controls for *GSTT1* and *GSTM1* null polymorphisms. Among controls, 15% were homozygous null for *GSTT1*, whereas 50% were homozygous null for *GSTM1*. These frequencies were similar for each ethnic/racial stratum. Neither risk for cleft lip ± cleft palate nor for cleft palate was increased among infants homozygous null for *GSTM1* or homozygous null for *GSTT1* compared with reference genotypes (Table 1).

Twenty-five percent of control mothers and 35% of case mothers smoked tobacco in the periconceptional period. The overall risk with smoking was the same for cleft lip ± cleft palate (OR = 1.6; 95% CI = 1.1–2.4) and for cleft palate (1.6; 1.1–2.6) (additional raw data available with the electronic version of this article).

We investigated potential combined influences of infant *GST* null genotypes and maternal smoking during the periconceptional period.[20] Table 1 shows a 2-fold higher risk for cleft lip ± cleft palate among smoking mothers whose infants lacked *GSTT1* compared with the risk from smoking when the infant had at least one copy of *GSTT1*. Quantifying smoking as 1 to 19 cigarettes per day or ≥20 cigarettes per day, it was apparent that the increased risk from the fetal null genotype was particularly high (nearly 7-fold) among maternal smokers of ≥20 cigarettes per day, but this risk lacks precision. For isolated cleft palate and *GSTT1* null, there was less difference in risks.

TABLE 1. Risks of *GSTT1 and GSTM1* Genotypes Among Isolated Orofacial Cleft Cases and Effects of Maternal Smoking During Pregnancy

		***GSTT1* Genotypes**		***GSTM1* Genotypes**		***GSTT1* and *GSTM1* Genotypes**	
	No.	**+/+ or +/Null OR (95% CI)**	**Null/Null OR (95% CI)**	**++ or +/Null OR (95% CI)**	**Null/Null OR (95% CI)**	**Any + Allele OR (95% CI)**	**Both Null/Null OR (95% CI)**
Isolated cleft lip ± cleft palate							
All*	297	1.0	1.1 (0.70–1.7)	1.0	0.99 (0.71–1.4)	1.0	1.1 (0.64–2.0)
Nonsmokers†	191	1.0	0.93 (0.55–1.6)	1.0	0.87 (0.59–1.3)	1.0	0.87 (0.42–1.8)
Smokers	106	1.5 (1.0–2.2)	2.9 (1.2–7.2)	1.4 (0.83–2.3)	1.8 (1.1–2.9)	1.5 (1.0–2.3)	6.3 (1.3–42)
Cigarettes per day							
1–19	76	1.4 (0.89–2.1)	2.3 (0.84–6.2)	1.5 (0.85–2.7)	1.3 (0.77–2.2)	1.4 (0.90–2.1)	4.0 (0.75–28)
≥20	30	2.1 (1.0–4.3)	6.9 (0.82–57)	1.1 (0.45–2.6)	6.8 (2.0–24)	2.1 (1.0–4.4)	∞
Isolated cleft palate							
All*	125	1.0	1.0 (0.57–1.8)	1.0	0.78 (0.50–1.2)	1.0	0.59 (0.23–1.4)
Nonsmokers†	82	1.0	0.93 (0.55–1.6)	1.0	0.70 (0.41–1.2)	1.0	0.89 (0.33–2.3)
Smokers	43	1.5 (0.89–2.5)	2.3 (0.61–8.2)	1.4 (0.70–2.7)	1.3 (0.65–2.6)	1.5 (0.97–2.6)	13 (0.02–26)
Cigarettes per day							
1–19	29	1.2 (0.67–2.2)	2.2 (0.57–8.6)	1.4 (0.63–3.0)	0.94 (0.44–2.0)	1.3 (0.75–2.3)	1.3 (0.02–26)
≥20	14	2.7 (1.1–6.5)	2.7 (0–99)	1.5 (0.48–4.4)	5.4 (1.2–27)	2.7 (1.1–6.3)	—

*Reference group for analysis of all infants.
†Reference group for maternal smoking analyses.
+GST gene intact; null indicates GST allele is deleted.
Numbers of cases and controls for this analysis are available with the online version of this article.

For *GSTM1*, Table 1 shows minimal differences in odds ratios between homozygous null infants and infants who had at least one copy of the gene for each of the cleft groups. Unlike *GSTT1*, there is little difference in risks for cleft lip ± cleft palate among smoking mothers whose infants lacked *GSTM1* compared with the risk from any amount of smoking when the infant had at least one copy of *GSTM1*. However, mothers who smoked ≥20 cigarettes per day had a nearly 6-fold higher risk for isolated cleft lip ± cleft palate when the fetus was homozygous null for *GSTM1*. Similarly, the risk for isolated cleft palate was 3 to 4 times higher when the fetus was homozygous null for *GSTM1*, but these odds ratios were less precise.

Among controls, 7.8% were combined homozygous null for both *GSTT1* and *GSTM1* compared with 9.1% of cleft lip ± cleft palate and 6.4% of cleft palate cases. Table 1 shows a 4-fold higher risk for cleft lip ± cleft palate for infants who were homozygous null for both GSTs, whereas data for isolated cleft palate were too sparse to draw interpretations. When we investigated the risks associated with absence of either *GSTT1* or *GSTM1*, the results were very similar to those shown in Table 1 (results not shown).

We also analyzed passive smoking exposures, limited to those mothers who did not smoke during the periconceptional period. ORs for cleft lip ± cleft palate from any passive smoke exposure (home or workplace) were 1.5 (95% CI = 0.80–2.9) for infants who were homozygous *GSTT1* null compared with 1.3 (0.84–2.0) for infants who had at least one *GSTT1* gene. For cleft palate and passive smoking exposure, the results were similar: OR = 1.6 (0.67–3.9) for infants who were homozygous *GSTT1* null and OR = 1.7 (0.92–3.0) for infants who had one or more copies of *GSTT1*. For *GSTM1* genotypes, we observed no difference in risks for passive smoking; infants with cleft lip and homozygous null for *GSTM1* had an OR = 1.3 (CI 0.77–2.3), whereas those with at least one copy of *GSTM1* had an OR = 1.4 (0.83–2.5). For cleft palate and *GSTM1* genotypes, we observed a slightly lower risk for passive smoking exposure: infants homozygous null for *GSTM1* genotype had an OR = 1.6 (0.71–3.8), whereas those with at least one copy of *GSTM1* had an OR = 2.8 (1.2–6.3).

DISCUSSION

We previously reported that maternal cigarette smoking during early pregnancy increased risks for both isolated cleft lip ± cleft palate and isolated cleft palate.[2] The increased risks were relatively modest (OR = 1.7) and were higher for mothers who smoked ≥20 cigarettes per day. The present study was designed to determine whether null polymorphisms of 2 glutathione *S*-transferases made the fetus more susceptible to the effects of smoking. Neither GST null polymorphism was an independent risk factor for isolated oral clefts. When we assessed potential interactions between the known smoking risks and *GSTT1* and *GSTM1* null polymorphisms, however, we found higher risks associated with absence of one or both of these xenobiotic metabolizing enzymes among infants born to smoking mothers. Among infants born to smoking mothers, the risk for cleft lip was doubled for fetuses who were homozygous null for *GSTT1* or *GSTM1* compared with fetuses who had a least one functional copy of a GST gene. In addition, our findings suggest that for the heaviest smokers, the magnitude of increased risk was nearly 6- and 7-fold for *GSTT1* null and *GSTM1* null genotypes, respectively—substantially higher than the 1.7-fold risks with smoking in the absence of any genotypic information. Among nonsmoking mothers, we saw no modification of risk for passive exposure to smoking and GST null polymorphisms.

Our findings confirm and extend suggestive results of a smaller Dutch study of 100 nonsyndromic orofacial cleft cases. Van Rooij and colleagues[16] reported a 5-fold increased risk for all clefts combined (OR = 4.9; 95% CI = 0.7–37) among smoking mothers when both mother and infant were *GSTT1* null. The frequency of homozygous *GSTT1* null genotype among these Dutch mothers (26%) and infants (37%) was higher than the 15% that we observed. The frequencies of *GSTT1* null genotypes in U.S. studies range from 15% to 27% for whites, 22% to 29% for blacks, and 10% to 12% for Hispanics.[21] In the United States, the frequency of *GSTM1* null genotype is approximately 51% among western European descendants, 46% among Hispanics, 59% among Asians, and 29% among blacks.[22]

Maternal metabolism of toxins in tobacco smoke clearly influences fetal exposures, and without the maternal genotypic information, we have an incomplete picture of all of the components of detoxification in utero. Because embryonic and maternal genotypes are correlated, it is possible that part of the effect we detected may result from the maternal genotype.

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Alternative Modes for Health Surveillance Surveys: *An Experiment with Web, Mail, and Telephone*

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Background: Web and mail surveys as complements to telephone surveys may help resolve concerns about declining participation in telephone surveys for public health surveillance. Little is known, however, about how responses obtained in Web surveys compare with those from mail or telephone surveys.

Methods: The Behavioral Risk Factor Surveillance System 2003 core interview was conducted in 3 survey modes: Web (n = 1143), mail (n = 836), and telephone (n = 2072). All 3 samples were drawn randomly. We compared respondent demographics and responses to 8 key questions on health conditions and risk behaviors (including asthma, diabetes, obesity, and HIV testing) across the 3 survey modes.

Results: Demographic characteristics of mail and Web respondents varied considerably from those interviewed by telephone. The unadjusted prevalence of outcomes varied by survey mode. After adjustment for respondent demographic characteristics, there were still differences among survey modes in several of the health conditions and risk behaviors, although for some of these, the pattern was different for the unadjusted and adjusted results.

Conclusions: As health surveys take advantage of new technologies and moved towards mixed-mode designs, researchers need to test for and, if necessary, account for the effect of mode in the estimates they produce.

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Web and mail surveys can help to increase response rates for random-digit-dialed (RDD) telephone surveys by broadening the mix of participants and improving data quality.[1,2] Different survey modes can, however, produce varying results even with identical questions, thereby potentially increasing measurement differences.[3,4] A number of research efforts have compared responses obtained by telephone, mail, and face-to-face surveys; however, our understanding of how Web surveys fit into this mix is quite limited.[5,6] We examined the potential impact of survey mode on estimates obtained in a major health surveillance. The findings are from a set of experiments conducted in 4 states to examine how responses to a health survey (the Behavioral Risk Factor Surveillance System) compare when administered over the Internet, by mail, and by telephone.

METHODS

As one of the world's largest RDD computer-assisted telephone interview (CATI) health surveys, the Behavioral Risk Factor Surveillance System collects uniform, state-specific data on preventive health practices and risk behaviors linked to morbidity and mortality among adults. Further details on survey design, methodology, and questionnaire are available at http://www.cdc.gov/brfss.

Two sets of experiments were conducted in each of 4 survey states (Arkansas, Indiana, New York, and North Dakota) during a 2-month timeframe (October and November 2003). In the first, we mailed invitations asking participants to complete the survey on the Internet. In the second, we mailed questionnaires to be completed and returned. The experiments were conducted in parallel with the regular, state RDD data collection to allow comparison of results across the 3 modes. Samples for the Web and mail experiments were drawn randomly from the RDD sampling frame. After reverse-matching telephone numbers to addresses, only those with addresses could be included in the 2 mailings. Therefore, only address-matched cases from the CATI survey are used for comparison. Within-household selection for the Web and mail surveys was accomplished by asking households to select an adult age 18 years or older to complete the survey. Questions were worded identically for all 3 modes. Data collection procedures were approved by Research Triangle Institute's Institutional Review Board (IRB). More details on the experiment design are available elsewhere.[7]

Dichotomous measures of chronic health conditions (asthma, diabetes, high blood pressure, and obesity) and risk behaviors (smoking, binge drinking, talking with a doctor about sexually transmitted disease [STD] prevention, and HIV testing) were examined. Asthma, diabetes, and high blood pressure were assessed by asking, "Have you ever been told by a doctor, nurse, or other health professional that you have [condition]?" Body mass index (BMI) was based on self-reported height and weight. Respondents were classified as obese if their BMI was $\geq$30 kg/m^2. Respondents who said that they currently smoke everyday or some days were classified as "current smokers." Binge drinking was assessed by asking, "Considering all types of alcoholic beverages, how many times during the past 30 days did you have 5 or more drinks on an occasion?" The final 2 variables were based on the questions, "In the past 12 months has a doctor, nurse or other health professional talked to you about preventing sexually transmitted diseases through condom use?" and "Have you ever been tested for HIV?"

In the analysis, the relationship between survey mode and demographic characteristics of respondents were examined through pairwise contingency tables. Next, a similar approach was used to examine the bivariate relationship between survey mode and the 8 measures of health condition and risk behavior. Finally, logistic models were developed for each of the health indicators to examine whether mode affected responses after adjusting for the impact of background characteristics.

RESULTS

A total of 4051 completed interviews were analyzed: 1143 Web, 836 mail, and 2072 CATI. The response rate for

TABLE 1. Respondent Characteristics by Survey Mode

	Survey Mode		
Characteristic	CATI (n = 2072) % (95% CI)	Mail (n = 836) % (95% CI)	Web (n = 1143) % (95% CI)
Sex			
Male	42 (40–44)	35 (31–38)	36 (34–39)
Female	58 (56–60)	65 (62–69)	64 (61–67)
Race			
White, non-Hispanic	86 (85–88)	92 (90–94)	93 (92–95)
Other	14 (12–15)	8 (6–10)	7 (6–9)
Age (years)			
18–34	20 (18–21)	10 (8–13)	15 (13–17)
35–49	30 (28–32)	28 (25–31)	37 (34–40)
50–64	27 (26–29)	29 (26–33)	33 (31–36)
65+	23 (22–25)	32 (29–36)	15 (13–17)
Education			
High school or less	44 (42–46)	37 (34–41)	24 (21–26)
Some college or more	56 (54–58)	63 (59–66)	76 (74–79)
Number of adults in household			
1	32 (30–34)	28 (25–32)	20 (17–22)
2	57 (55–59)	59 (56–62)	61 (58–64)
3+	11 (10–12)	13 (11–15)	19 (17–22)

TABLE 2. Unadjusted Prevalence Estimates and Adjusted Odds Ratios for Effects of Survey Mode on Self-Reports of Health Conditions and Risk Factors

	Unadjusted Prevalence Estimates			Adjusted Odds Ratios*		
Health Condition/ Risk Factor	CATI % (95% CI)	Mail Survey % (95% CI)	Web Survey % (95% CI)	CATI†	Mail Survey AOR (95% CI)	Web Survey AOR (95% CI)
Asthma	11.7 (10.3–13.1)	12.0 (9.8–14.2)	11.9 (10.0–13.8)	1.0	1.07 (0.84–1.34)	1.06 (0.83–1.38)
Diabetes	9.5 (8.2–10.8)	11.9 (9.7–14.1)	10.2 (8.4–12.0)	1.0	1.16 (0.89–1.51)	1.30 (1.01–1.67)
High blood pressure	31.1 (29.1–33.1)	38.1 (34.8–41.4)	33.2 (30.5–35.9)	1.0	1.22 (1.01–1.46)	1.30 (1.09–1.54)
Obese (BMI >30)	21.6 (19.8–23.4)	26.5 (23.5–29.5)	25.6 (23.0–28.2)	1.0	1.37 (1.12–1.66)	1.31 (1.10–1.57)
Current smoker	22.8 (21.0–24.6)	16.9 (14.4–19.4)	17.3 (15.1–19.5)	1.0	0.83 (0.67–1.03)	0.77 (0.63–0.93)
Binge drinking	14.4 (12.9–15.9)	12.3 (10.1–14.5)	21.6 (9.0–24.2)	1.0	1.17 (0.90–1.52)	1.87 (1.50–2.34)
STD prevention‡	8.2 (6.8–9.6)	4.3 (2.6–6.0)	3.3 (2.2–4.4)	1.0	0.69 (0.43–1.12)	0.51 (0.33–0.78)
Tested for HIV‡	38.8 (36.3–41.3)	30.8 (27.0–34.6)	32.1 (29.1–35.1)	1.0	0.81 (0.65–1.01)	0.85 (0.71–1.03)

*Models are adjusted for respondents' state of residence, sex, race, age, education, and number of adults in the household.
†CATI is reference category.
‡Questions not asked of respondents age 65 yr or older.

the Web survey was 15% compared with 44% for the mail survey and 40% for CATI.[8]

Respondent Demographics

Characteristics of survey respondents varied considerably across modes (Table 1). Web and mail respondents were more likely to be female and white than CATI respondents. The percentage of respondents age 65 years or older was highest among mail respondents. The percentage who had attended college was highest for Web respondents, intermediate for mail respondents, and lower for CATI respondents. Web respondents were also more likely to live in households with 3 or more adults.

Health Outcomes

The unadjusted prevalence estimates for asthma and diabetes showed little evidence of difference by survey mode (Table 2). In contrast, a higher percentage of mail respondents reported having high blood pressure. These findings are not surprising given the age distributions across the survey modes. Respondents who completed the self-administered modes (mail or Web) were also more likely to be obese compared with CATI respondents.

Self-reported binge drinking was higher among Web survey respondents than among either mail or telephone (CATI) respondents (Table 2). This finding is consistent across age groups for both men and women (data not shown). Respondents to the self-administered modes were less likely than CATI respondents to report currently being a smoker, having talked to a doctor about STD prevention, or having ever been tested for HIV (Table 2).

After adjusting for respondent characteristics, the effect of mode becomes less clear but did not disappear. For the binge drinking and STD prevention items, telephone and Web represent the extremes in responses. When comparing Web responses with CATI, the odds of a "yes" response increased by 87% for binge drinking and decreased by 49% for having talked with a doctor about STD prevention. In contrast, there was little difference by mode for asthma, diabetes, and HIV testing. For high blood pressure and obesity, self-administered survey respondents (mail or Web) were more likely to have answered affirmatively; for the question on current smoking, the mail and Web respondents were less likely than telephone respondents to answer affirmatively.

DISCUSSION

The types of people who responded to the Web, mail, and telephone surveys varied considerably across these 3 modes. As a result, it should not be surprising that the crude responses to the health and risk questions varied across these modes. However, mode-related effects persisted even after adjusting for demographic differences. These persistent mode differences were most notable among Web survey respondents. Although these findings may reflect true mode effects, there may also be residual confounding by unmeasured or measured demographic factors. From a more practical standpoint, however, the results indicate that differences appear to persist in some measures even after adjusting for variables typically used in poststratification weighting for most health surveys (ie, sex, race, age, education).

The findings need to be evaluated within the context of the study's limitations. First, we included only those cases for which a valid address could be matched to the randomly drawn telephone number. Second, although using the survey RDD sampling frame allowed us to make more valid comparisons of mail and Web results with the telephone survey data, it may have limited the use of the mail and Web approaches. For example, approximately one third of those interviewed in a telephone follow up of Web nonrespondents indicated that they did not complete the Web survey because they did not have access to the Internet.[9] Third, in the absence of more direct measures (such as patient records or medical tests), we cannot determine which mode is the most accurate. We know only that strong differences exist in the measures obtained using these various modes. Finally, the study was conducted in 4 states, which may not be representative of either the nation or other populations.

In conclusion, mode of interview affects the estimates produced. However, as this study shows, the impact of mode can be unpredictable. For some measures, mode had a strong effect, whereas for others, there was minimal evidence of mode effects. Additionally, the direction of the impact (positive or negative) is not clearcut across health measures. As health surveys take advantage of new technologies such as the Web, and move toward combinations of modes to address concerns over low participation, researchers need a better understanding of when and how mode can impact their estimates. At a minimum, they need to test and, if necessary, account for the effects of mode in the models and estimates they report.

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Risk Factors for Work-Related Assaults on Nurses

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Background: Work-related homicides have been the subject of considerable study, but little is known about nonfatal violence and relevant risk factors.

Methods: We surveyed 6300 Minnesota nurses who were selected randomly from the 1998 licensing database and determined their employment and occupational violence experience. In a nested case–control study, we examined environmental exposures and physical assault. Cases of assault in the previous 12 months and controls randomly selected from assault-free months were surveyed about prior-month exposures.

Results: After adjustment by multiple logistic regression, incidence of physical assault was 13.2 per 100 persons per year (95% confidence interval = 12.2–14.3). Among 310 cases and 946 control subjects, odds ratios for assault were increased: in nursing homes or long-term care facilities (2.6; 1.9–3.6), emergency departments (4.2; 1.3–12.8), and psychiatric departments (2.0; 1.1–3.7); in environments not "bright as daylight" (2.2; 1.6–2.8); and for each additional hour of shift duration (1.05; 0.99–1.11). Risks were decreased when carrying cellular telephones or personal alarms (0.3; 0.2–0.7).

Conclusions: These results may guide in-depth investigation of ways protective and risk factors can control violence against nurses.

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Violence is a major public health problem,[1] particularly important in the work environment. Homicide is the third-leading cause of occupational fatality and the second-leading cause of occupational fatality for women.[2] Although much is known about work-related homicides, research on nonfatal violence and relevant risk factors is limited. Nearly

2 million acts of nonfatal work-related violence occur annually in the United States alone.[3]

Hospital and health care workers are at high risk for violence, particularly nonfatal violence.[4,5] Violence against nurses specifically is a major occupational health problem.[6–9] On the basis of the 1992 Minnesota Workers' Compensation files, nurses accounted for more than 7% of the total work-related assault cases leading to more than 3 days of lost time; women's assault rate was twice that of men.[10] Biologic,[11] psychologic,[12] and sociocultural[13] theories have been generated to explain causes of violence. Understanding the factors that place persons at risk for violence is critical to development of effective interventions. The current study, following up on a smaller case–control study,[14] was designed to identify environmental and other exposures associated with the risk of work-related violence. Such factors may provide a basis for interventions to reduce the risk of work-related violence.

METHODS

Study Population

Licensing is required for both registered nurses (RNs) and licensed practical nurses (LPNs) who practice in Minnesota. The target population was defined as licensed RNs and LPNs who had worked in Minnesota during the 12 months before the date they completed the survey. With approval by the University of Minnesota Institutional Review Board, we randomly sampled 6,300 nurses from the population (n = 79,128) of currently active RNs (n = 57,388) and LPNs (n = 21,740) who were licensed in the state of Minnesota as of 1 October 1998. Besides name, license type, and address, the state database included birth date, sex, and year of first licensure.

Selection of Cases and Control Subjects

We initially mailed a questionnaire to the entire sample of 6300 nurses to determine employment status and the incidence and consequences of work-related violence.[15] On the basis of the responses, we identified 475 cases (those who reported at least 1 event of physical violence during the previous 12 months) and 1425 control subjects. Control subjects were selected randomly from all months during the study period in which the nurses indicated having worked but before any reported physical assaults to those nurses. This sampling method ensured that the distribution of sampled calendar months represented the distribution of months worked.

Definitions

Physical assault was defined as being hit, slapped, kicked, pushed, choked, grabbed, sexually assaulted, or otherwise subjected to physical contact intended to injure or harm. Violence was work-related if it occurred in the work environment or during any activities associated with the job (including travel). This is consistent with the definition used by the U.S. National Institute for Occupational Safety and Health (NIOSH).[16]

Exposures Addressed

We assessed exposures based on previous research on violence and evidence from other areas of the injury epidemiology literature.[17] General exposures included work experience (years worked as a licensed nurse; years worked in department), average patient contact hours per shift, average number of nurses and number of overall staff located in the immediate work environment on the shift worked most often, primary facility and department/unit/area worked, the main patient population, and primary professional activity. Factors pertinent to environmental design included accessibility of exits and physical barriers preventing view of others in the work environment and level of lighting. Environmental protection factors (assault deterrents in the immediate work environment) included video monitor, metal detector, security alarm/panic button, controlled access, security personnel, or escort/body guard. Personal protection factors included cellular telephone and personal alarm.

Data Collection

For both the initial survey and the nested case–control study, we sent up to 4 follow-up mailings. These mailings included a cover letter providing information for participant consent, together with the pertinent survey, and a postage-paid return envelope.

Contact Procedures

Initial Survey

The initial survey collected the following data: (1) months in which the nurses worked in a nursing position in the previous 12 months; (2) demographic information; and (3) information on physical and nonphysical work-related violence events during the study period. Overall, 79% responded (an estimated 78%, adjusting for the estimated eligible fraction among nonrespondents for age, gender, license-type, and location).[18,19] The response rates for RNs and LPNs, respectively, were 81% (79%, adjusted) and 75% (73%, adjusted).[15]

Case–Control Study

A conceptual model based on a priori hypotheses served as the foundation for a causal model[20] that in turn guided survey design and analysis.[21,22] The survey questionnaire ascertained exposures for the month before and during the incident itself for cases; if multiple events were reported, cases were surveyed about the month before the earliest event. For controls the questionnaire ascertained exposures for random months, selected as described above. Question-

TABLE 1. Demographic and Occupational Characteristics of Cases and Controls

	Cases (n = 310)	Controls (n = 946)
Sex; %		
Women	95	96
Men	6	4
Age (years); %		
<30	7	6
30 to 39	19	14
40 to 49	39	39
50 to 59	26	30
60+	9	10
Practice type; %		
RN	69	74
LPN	31	26
Nursing education; %		
Diploma	39	38
Associate Degree	38	27
Bachelor's Degree	21	27
Master's or Doctorate Degree	1	6
Missing	1	2
Type of Facility; %		
Hospital in-patient	42	41
Nursing home/long-term care/rehabilitation	46	17
Hospital/Non-Hospital outpatient	4	9
Clinic/health care provider office	3	13
Other*	5	21
Missing	0	<1
Department/unit/area; %		
Medical/surgical; obstetrics/gynecology	23	28
Emergency	4	3
Psychiatric/behavioral	11	6
Intensive care unit	9	7
Long-term/assisted care	40	15
Other†	14	41
Missing/Refused	0	<1
Primary patient population; %		
Adult	36	44
Geriatric	47	22
Neonatal, Pediatric, Adolescent	4	14
Split time	14	20
Missing/refused	0	1
Average patient length of stay; %		
<1 day	6	23
1–<4 days	14	18
4 days to <1 week	15	13
1 week to <2 weeks	6	5
2 weeks to <3 weeks	2	2
3 weeks to <1 month	3	2
1 month or more	44	26
Unsure	9	9
Missing/refused	1	1
Primary professional activity; %		
Provided patient care	68	62
Supervised patient care	16	8
No patient care‡	17	30
Missing	0	<1
Years in department, mean ± SD	7.9 ± 7.2	9.1 ± 8.2
Years as Licensed Nurse, mean ± SD	15.9 ± 10.6	18.4 ± 10.8
Patient contact hours, mean ± SD	5.5 ± 2.5	4.9 ± 3.2
No. personnel on shift; mean ± SD	11.0 ± 9.9	12.7 ± 13.7
Number of nurses on shift, mean ± SD	7.4 ± 5.9	8.0 ± 9.4

*Home/public health agency; school/college/university; independent practice/consulting; insurance/utilization review; industry; split time.
†Operating/recovery; public health/home care; family practice; occupational health; school health; education/research; split time.
‡Administration; teaching; research; case management; insurance/utilization review; telephone triage/health information; split time.

naires specific to the respective month were sent to all participants.

Analyses

We obtained responses to the full case-control questionnaire from 324 cases (68%) and 946 control subjects (66%). However, we focused primarily on patient- or client-initiated work-related assaults (310 cases, 96% of all physical assaults). For each exposure of interest, we selected confounders for multiple logistic regression using the principles in Maldonado and Greenland,[23] and based on directed acyclic graphs.[20–22] These methods identify parsimonious models and exclude covariates that should not be entered into the regression because they could introduce bias.

To account for variability from sampling and also from uncertainty about adjustment weights and eligibility fractions, we calculated bootstrap confidence intervals (CIs)[24] for all odds ratios. Potential response bias was controlled by inversely weighting observed responses by probabilities of response,[25] estimated as a function of the following characteristics available from the licensing database: age; sex; license type; and type of home address (metropolitan versus nonmetropolitan). To adjust the weighting for unknown eligibility among nonrespondents, we estimated the probability of eligibility from these same factors.[18] The entire weighting

TABLE 2. Univariate and Multivariate Analyses of Occupational Exposures and Risk of Physical Assault

	Unadjusted OR (95% CI)	Partially Adjusted* OR (95% CI)	Fully Adjusted† OR (95% CI)
Years worked as licensed nurse			
Change per 10 years	0.83 (0.73–0.94)	0.92 (0.78–1.09)	0.90 (0.76–1.06)
Years worked in department			
Change per 10 years	0.83 (0.69–1.01)	0.91 (0.74–1.11)	0.91 (0.74–1.11)
Patient contact hours per shift			
Change per hour	1.07 (1.03–1.12)	1.06 (1.00–1.12)	1.05 (0.99–1.11)
Number of nursing personnel on shift			
Change per 10 nurses	0.95 (0.81–1.11)	0.90 (0.72–1.12)	0.96 (0.75–1.17)
Number of all personnel on shift			
Change per 10 personnel	0.91 (0.81–1.02)	0.93 (0.81–1.08)	0.98 (0.83–1.14)
Facility			
Hospital in-patient‡	1.0	1.0	1.0
Nursing home/long term care/ rehabilitation	2.62 (1.94–3.54)	2.68 (1.98–3.63)	2.64 (1.91–3.60)
Hospital-outpatient/nonhospital outpatient	0.39 (0.20–0.75)	0.40 (0.20–0.77)	0.39 (0.20–0.77)
Clinic/health care provider	0.22 (0.11–0.45)	0.23 (0.11–0.46)	0.24 (0.11–0.54)
Other§	0.24 (0.14–0.41)	0.24 (0.14–0.42)	0.24 (0.14–0.43)
Department			
Medical/Surgical; Obstetrics/Gynecology‡	1.0	1.0	1.0
Emergency	1.88 (0.90–3.94)	4.19 (1.63–10.77)	4.22 (1.33–12.79)
Psychiatric/Behavioral	2.24 (1.36–3.69)	2.01 (1.18–3.44)	2.03 (1.05–3.73)
Intensive Care	1.56 (0.93–2.63)	1.34 (0.79–2.27)	1.18 (0.64–1.98)
Long-term/assisted care	3.19 (2.24–4.55)	0.98 (0.48–2.01)	1.02 (0.47–2.60)
Other§	0.42 (0.28–0.63)	0.69 (0.43–1.10)	0.78 (0.49–1.34)
Primary patient population			
Adult‡	1.0	1.0	1.0
Neonatal, pediatric, adolescent	0.38 (0.21–0.71)	0.44 (0.23–0.83)	0.44 (0.22–0.99)
Geriatric	2.64 (1.96–3.56)	1.56 (0.92–2.63)	1.50 (0.85–2.58)
Split time	0.85 (0.58–1.26)	1.11 (0.72–1.71)	1.02 (0.57–1.59)
Primary professional activity			
No patient care‡,§	1.0	1.0	1.0
Provided patient care	2.00 (1.42–2.78)	1.58 (1.04–2.40)	1.49 (0.89–2.31)
Supervised patient care	3.80 (2.38–6.08)	1.61 (0.95–2.74)	1.51 (0.75–2.52)
Environmental lighting/design			
Less than bright as daylight(vs. bright as daylight)	2.06 (1.57–2.70)	2.22 (1.68–2.94)	2.15 (1.58–2.83)
Easily accessible exits (yes vs. no)	0.84 (0.47–1.52)	0.94 (0.51–1.71)	0.96 (0.50–1.78)
Physical barriers blocking vision (yes vs. no)	1.33 (1.03–1.73)	1.32 (1.01–1.73)	1.25 (0.91–1.63)
Environmental protection (yes vs. no)			
Video monitor	1.22 (0.86–1.73)	1.01 (0.65–1.57)	1.14 (0.63–1.83)
Metal detector	1.40 (0.53–3.71)	0.92 (0.30–2.87)	0.92 (0.17–3.93)
Security alarm/panic button	1.45 (1.08–1.94)	1.45 (1.01–2.08)	1.56 (0.96–2.39)
Controlled access	0.87 (0.67–1.14)	0.90 (0.65–1.26)	0.94 (0.62–1.43)
Security personnel	0.68 (0.52–0.88)	0.96 (0.66–1.40)	0.90 (0.59–1.42)
Escort/body guard provided by any source	0.61 (0.46–0.82)	0.80 (0.55–1.16)	0.84 (0.53–1.36)
Escort/body guard provided by employer	0.64 (0.48–0.86)	0.83 (0.57–1.21)	0.86 (0.53–1.41)

(Continued)

TABLE 2. *(Continued)*

	Unadjusted OR (95% CI)	Partially Adjusted* OR (95% CI)	Fully Adjusted† OR (95% CI)
Personal protection (yes vs. no)			
Carry personal protection	0.83 (0.57–1.21)	0.88 (0.60–1.31)	0.89 (0.60–1.41)
Nurse provided own cellular telephone/personal portable alarm	0.33 (0.18–0.61)	0.30 (0.16–0.58)	0.30 (0.15–0.71)
Cellular telephone/personal portable alarm provided by employer	1.01 (0.71–1.44)	1.03 (0.70–1.50)	1.01 (0.70–1.54)

*Partially Adjusted Model adjusts for confounders, as follows: (1) for years worked as licensed nurse and years worked in department: gender, age, education; (2) for patient contact hours: staffing, professional activity, number of patients, hours worked per month; (3) for number of nursing personnel on shift and number of all personnel on shift: number of patients, policies, administrators' attitudes, primary facility, primary department (4) for facility: gender, race; (5) for department: gender, facility; (6) for primary patient population: gender, race, facility, department; (7) for primary professional activity: gender, age, race, marital status, license type, years worked as licensed nurse, years worked in department, primary facility, primary department, patient population; (8) for environmental lighting/design: video monitor, metal detection device, security alarm, controlled access, security personnel, escort/body guard; (9) for environmental protection: primary department, primary patient population, policies, training, hours worked per month, personnel and patient demographics, patient contact hours, average length of patient stay, patient impairment status; and (10) for personal protection: video monitor, metal detection device, security alarm, controlled access, security personnel, escort/body guard, morale, personnel respect/trust level.

†Fully Adjusted Model adjusts for confounders, as noted for the Partially Adjusted Model; in addition, the odds ratios and confidence intervals are calculated using weights to adjust for nonresponse and ineligibility.

‡Reference category.

§See details of "other" category in Table 1 footnotes.

procedure was recalculated on each bootstrap iteration. Validation procedures, reported elsewhere, were conducted for self-reported physical assault injury occurrences and various workplace exposures.[20] We conducted sensitivity analyses to determine the potential effect of an unmeasured confounder on the multivariate odds ratios.[20,26]

RESULTS

On the basis of the initial survey, 96% of nurses were women. On average, participants were 46 years of age (±SD, 10.1); 75% were RNs, and the rest were LPNs. The estimated physical assault rate was 13.2 per 100 persons per year (95% CI = 12.2–14.3). The assault rate was lower for RNs (12.0; 10.9–13.3) than for LPNs (16.4; 14.2–18.7).[15]

Characteristics of cases and controls are shown in Table 1. Cases and control subjects were similar by sex and age. Cases were less likely to have bachelor's degrees or higher and more likely to be working primarily in nursing homes or long-term care facilities and with geriatric patients.

Table 2 provides risk estimates at 3 levels of analyses: unadjusted; partially adjusted for a minimal set of confounders[20,21]; and the corresponding fully adjusted multivariate analysis, weighted for nonresponse and unknown eligibility.

Nurses at greatest risk of assault were those working in nursing homes or long-term care facilities (2.6; 1.9–3.6) and emergency (4.2; 1.3–12.8) and psychiatric (2.0; 1.1–3.7) departments. Risk increased for each additional hour of shift duration (1.05; 0.99–1.11).

Of all the environmental factors, the amount of lighting was most strongly associated with risk. The odds of assault were doubled when lighting was less bright than daylight (2.2; 1.6–2.8). Other elements of environmental protection (such as video monitors and security personnel) had little apparent effect. Risk was substantially reduced among nurses who provided their own cellular telephones or portable alarms (0.30; 0.15–0.71). However, cellular telephones provided by the employer provided no apparent protection (1.0; 0.70–1.5).

DISCUSSION

We found increased risks of work-related physical assault among nurses who worked in nursing home or long-term care facilities and also among those working in psychiatric and emergency departments. Other studies[27,28] have identified similar risks using designs different from the present study. We also found increased risk of assault in environments that were not fully illuminated. A previous case–control study of occupational homicide has identified reduced risks with bright exterior lighting;[29] however, the importance of interior lighting had apparently not been considered. Although every hour of patient contact increased risk at least 5%, both nursing and total staffing might moderate this risk. Further research may confirm this finding. The lower risk among nurses carrying their own cellular telephone or personal portable alarm is apparently not due to the availability of the telephone itself, since those provided by employers conferred no protection.

Our information on both the exposures and the outcome was based on self-report, which is a potential weakness. We attempted to minimize this bias by limiting the recall of violent events to the previous 12 months[30] and the recall of exposures to a 1-month period within the preceding year,[14] as has been done in previous studies. To further minimize information bias, nurses were contacted again by mail to clarify ambiguous or missing information.[20] We also conducted validation substudies of environmental exposures and health care treatment.[20] Potential response bias was controlled for by Horvitz and Thompson reweighting[25] using weights adjusted for the probability of being eligible among nonrespondents.[18] Sensitivity analyses conducted on key exposures of interest[26] suggest that the results are not due to unmeasured confounding.[20]

In summary, we estimated the incidence of violence in licensed nursing professionals, a large occupational population, and identified relevant risk and protective factors. These results can guide further investigation of relevant factors, and perhaps lead to effective methods for reducing the substantial risk of physical assault in health care settings.

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