

## CORRESPONDENCE

### Re: Medical History Risk Factors for Non-Hodgkin's Lymphoma in Older Women

Cerhan et al. (1) reported a twofold increased risk of non-Hodgkin's lymphoma (NHL) among older women with adult onset of diabetes mellitus. We would like to provide data from a large Swedish cohort of patients with diabetes mellitus that (may) further characterize the hypothesized association with NHL.

The methodology used in this study is published elsewhere (2). In brief, 153 852 patients having diabetes mellitus as a hospital discharge diagnosis in Sweden from 1965 to 1983 were followed for occurrence of cancers through 1989 by linkages of nationwide registries. To minimize the impact of selection bias, we excluded the first year of follow-up from all analyses (153 852 person-years and 49 cases of NHL, corresponding to standardized incidence ratio of 1.70 [95% confidence intervals =

1.26-2.24]). Only first primary cancers were included in the analysis. Standardized incidence ratios (SIRs), standardized mortality ratios (SMRs), and 95% confidence intervals (CIs) were computed by use of nationwide NHL incidence and mortality rates. Information was not available to classify diabetes as insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM).

In this large population-based cohort study, we found a modest, statistically significant 18% excess incidence of NHL among patients hospitalized with diabetes mellitus. During 1-25 years of follow-up, 237 incident cases of primary NHL were identified in the cohort, yielding an overall SIR of 1.18 (95% CI = 1.04-1.34) (Table 1). There was no difference in the risk of NHL according to sex. The risk of NHL was not greater either for patients enrolled in the cohort before age 40 years (predominantly IDDM) or for cohort members born before 1900 and surviving until enrollment in the cohort (predominantly NIDDM). Furthermore, individuals ever hospitalized with diabetes mellitus complications (neuropathy, nephropathy, or retinopathy), who were likely to represent patients with poorer metabolic control leading to higher levels of insulin in

NIDDM, presented no statistically significant difference in the risk of NHL compared with those with no recorded hospitalization for such complications. In contrast to the study by Cerhan et al. (1), the relative risk of NHL continuously decreased with increasing time of follow-up. For patients with no comorbidity (having diabetes mellitus as their only discharge diagnosis at cohort entry), the SMR for NHL was 0.99 (95% CI = 0.70-1.40). For patients with comorbidity (any other discharge diagnosis besides diabetes mellitus at the index hospitalization), the SMR for NHL was 1.51 (95% CI = 1.30-1.70).

The main limitations of our study are lack of data on age at onset of diabetes mellitus and type of disease (NIDDM versus IDDM) and on treatment of diabetes. The strengths are the large study size, long duration of follow-up, and completeness of follow-up.

As much as there was an increased risk of NHL among patients with diabetes mellitus, the present observations are in accordance with those of Cerhan et al. (1). However, whereas the risk of NHL tended to increase with time since onset of diabetes in the American study, the opposite was observed in the present study. This would suggest that mechanisms other than those suggested by

**Table 1.** Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of NHL in patients with diabetes mellitus, by cohort characteristics\*

| Characteristic                                 | Entering the cohort | Person-years | No. of cases of NHL | SIR  | 95% CI    |
|--|---------------------|--------------|---------------------|------|-----------|
| Whole cohort                                   | 134 098             | 901 147      | 237                 | 1.18 | 1.04-1.34 |
| Sex  |                     |              |                     |      |           |
| Males  | 63 988              | 432 650      | 127                 | 1.18 | 0.98-1.40 |
| Females  | 70 110              | 468 497      | 110                 | 1.19 | 0.98-1.43 |
| Age entered cohort, y                          |                     |              |                     |      |           |
| <40  | 20 268              | 229 237      | 7                   | 0.98 | 0.39-2.02 |
| ≥40  | 113 830             | 671 910      | 230                 | 1.19 | 1.04-1.35 |
| Birth cohort                                   |                     |              |                     |      |           |
| <1900  | 25 367              | 99 673       | 37                  | 1.10 | 0.77-1.51 |
| ≥1900  | 108 731             | 801 474      | 200                 | 1.20 | 1.04-1.38 |
| Initial hospitalization                        |                     |              |                     |      |           |
| Diabetes as only diagnosis                     | 35 552              | 308 834      | 57                  | 1.26 | 0.95-1.60 |
| Diabetes as concomitant disease                | 98 546              | 592 313      | 180                 | 1.16 | 1.00-1.30 |
| Ever hospitalized with diabetic complications† |                     |              |                     |      |           |
| No   | 117 295             | 795 652      | 210                 | 1.16 | 1.01-1.32 |
| Yes  | 16 803              | 105 495      | 27                  | 1.42 | 0.93-2.06 |
| Follow-up, y                                   |                     |              |                     |      |           |
| 1-4  | 134 098             | 344 208      | 100                 | 1.32 | 1.07-1.60 |
| 5-9  | 97 736              | 360 019      | 99                  | 1.19 | 0.97-1.45 |
| 10-24  | 44 792              | 196 920      | 38                  | 0.91 | 0.65-1.25 |

\*Excluding the first year of follow-up and cases incidentally diagnosed at autopsy. Non-Hodgkin's lymphoma (NHL) = ICD-7 (International Classification of Diseases, 7th Revision) Nos. 200 and 202, except 200.2.

†Diabetic complications = retinopathy (ICD, 8th Revision [No. 260.21]), neuropathy (ICD, 8th Revision [No. 260.49]), and nephropathy (ICD, 8th Revision [No. 260.30]).

Cerhan et al. (1) may underlie the observed association between diabetes mellitus and NHL. Further studies are needed to establish more stable risk estimates and to clarify the mechanisms involved.

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## References

- (1) Cerhan JR, Wallace RB, Folsom AR, Potter JD, Sellers TA, Zheng W, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. *J Natl Cancer Inst* 1997;89:314-8.
- (2) Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekblom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst* 1996;88:1472-7.

## Notes

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## Use of an NK<sub>1</sub> Receptor Antagonist to Prevent Delayed Emesis After Cisplatin

Despite the use of serotonin antagonists, most patients continue to experience vomiting with chemotherapy, particularly delayed emesis. Substance P, a regulatory peptide (1), induces vomiting (2) and binds to the NK<sub>1</sub> neuroreceptor. Compounds that block the NK<sub>1</sub> receptor (3-6) lessen emesis after cisplatin, ipecac, copper sulfate, apomorphine, and radiation therapy (4,5). This broad activity suggests that substance P and the receptor may play central roles in emesis. We evaluated the NK<sub>1</sub> receptor antagonist CP-122,721 in 17 cancer patients receiving cisplatin ( $\geq 80$  mg/m<sup>2</sup> over <3 hours) that induces acute vomiting in 98% of the patients not receiving antiemetics (7) and delayed vomiting in 89% (8). CP-122,721 (1 mg/kg) prevented emesis after cisplatin in the ferret model that predicted the activity and dose of serotonin antagonists (9,10).

All 17 patients had a normal electrocardiogram, bilirubin level, and creatinine level and provided written informed consent. A single oral dose of CP-122,721 (50 mg [n = 3], 100 mg [n = 4], and 200 mg [n = 10]) was administered 30 minutes before cisplatin. Patients were observed for 24 hours for emesis, nausea (11), and side effects and were contacted later about delayed vomiting. Statistical tests were two-sided.

The initial 10 patients received prophylactic antiemetics together with CP-122,721. Eight patients had emesis with prior cisplatin and each received the same antiemetics. Seven patients, four who had not received cisplatin previously, received CP-122,721 alone as prophylaxis. Patient characteristics and results are shown in Table 1. Among the 10 patients receiving single CP-122,721 doses of 50-200 mg with antiemetics, 100% had no acute emetic episodes. Eighty percent reported no delayed emesis. Among the nine patients who had received cisplatin previously, 78% experienced no acute emesis in the prior course, and delayed emesis prevention rose from 11% to 78% with CP-122,721 ( $P = .007$ ). Five of the seven patients who received 200 mg of CP-122,721 alone as prophylaxis had two or fewer episodes, a significant difference compared with historical controls ( $P = .0001$ ) (7). With the use of the same control subjects (7), those receiving CP-

**Table 1.** Patients and results\*

| Patients                                    | No.*       |                  |   |
|---|------------|------------------|---|
| Median age, y (range)                       | 60 (38-75) |                  |   |
| Female                                      | 7          |                  |   |
| Male  | 10         |                  |   |
| Lung cancer                                 | 12         |                  |   |
| Other primary cancer                        | 5          |                  |   |
| Cisplatin dose $\geq 100$ mg/m <sup>2</sup> | 16         |                  |   |
| Results                                     | Total      | CP-122,721 alone | CP-122,721 + serotonin antagonist + dexamethasone |
| CP-122,721 cycle                            |            |                  |   |
| No. of patients                             | 17         | 7                | 10  |
| No acute emesis                             | 65%        | 15%              | 100%  |
| 0-2 acute episodes                          | 88%        | 71%              | 100%  |
| Acute nausea score                          | 0 mm       | 0 mm             | 0 mm  |
| No delayed emesis episodes                  | 83%        | 86%              | 80%   |
| Prior cisplatin cycle                       |            |                  |   |
| No. of patients                             | 12         | 3                | 9   |
| No acute emesis                             | 75%        | 66%              | 78%   |
| 0-2 acute episodes                          | 75%        | 66%              | 78%   |
| No delayed emesis episodes                  | 17%        | 33%              | 11%   |

\*Unless otherwise specified, values = number of patients.

122,721 alone had fewer vomiting episodes (mean, two versus seven) ( $P = .007$ ). Six (86%) of the seven patients who received one dose of CP-122,721 alone as prophylaxis reported no delayed emesis. Acute emesis and delayed emesis were similar among the CP-122,721 doses. No adverse effects of CP-122,721 occurred.

This trial reports the first use of a substance-P antagonist to prevent cisplatin-induced emesis. The most dramatic finding was the prevention of delayed vomiting in 83% of the patients given a single prophylactic dose of CP-122,721. Only 17% of previously treated individuals had no delayed emesis in their prior course ( $P = .006$ ). This observation that NK<sub>1</sub> receptor blockade prevents delayed emesis suggests that substance P may, in part, mediate this reflex. In patients receiving CP-122,721 alone as prophylaxis for acute cisplatin-induced emesis, vomiting was lessened compared with historical data (7), showing activity against acute emesis. For patients who had experienced acute emesis with a serotonin antagonist and dexamethasone in prior cycles, control during a subsequent cycle with CP-122,721 did not decline as expected (12). These data suggest that NK<sub>1</sub> antagonists may provide additive acute control. Further study of NK<sub>1</sub> receptor antagonists provides a singular opportunity to improve our understanding and control of emesis.

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## References

- (1) Dockray GJ. Substance P and other tachykinins. In: Walsh JH, Dockray GJ, editors. Gut peptides: biochemistry and physiology. New York: Raven Press, Ltd., 1994:401-15.
- (2) Knox AP, Strominger NL, Battles AH, Carpenter DO. Behavioral studies of emetic sensitivity in the ferret. *Brain Res Bull* 1993;31:477-84.
- (3) Snider RM, Constantine JW, Lowe JA 3d, Longo KP, Lebel WS, Woody HA, et al. A potent nonpeptide antagonist of the substance P (NK<sub>1</sub>) receptor. *Science* 1991;251:435-7.
- (4) Bountra C, Bunce K, Dale T, Gardner C, Jordan C, Twissell D, et al. Anti-emetic profile of a non-peptide neurokinin NK<sub>1</sub> receptor antagonist, CP-99,994, in ferrets. *Eur J Pharmacol* 1993;249:R3-4.

- (5) Watson JW, Gonsalves SF, Fossa AA, McLean S, Seeger T, Obach S, et al. The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK<sub>1</sub> receptor. *Br J Pharmacol* 1995;115:84-94.
- (6) Beattie DT, Beresford IJ, Connor HE, Marshall FH, Hawcock AB, Hagan RM, et al. The pharmacology of GR203040, a novel, potent and selective non-peptide tachykinin NK<sub>1</sub> receptor antagonist. *Br J Pharmacol* 1995;116:3149-57.
- (7) Kris MG, Cubeddu LX, Gralla RJ, Cupissol D, Tyson LB, Venkatraman E, et al. Are more antiemetic trials with placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. *Cancer* 1996;78:2193-8.
- (8) Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989;7:108-14.
- (9) Gonsalves S, Watson J, Ashton C. Broad spectrum antiemetic effects of CP-122,721, a tachykinin NK<sub>1</sub> receptor antagonist, in ferrets. *Eur J Pharmacol* 1996;305:181-5.
- (10) Florczyk AP, Schurig JE, Bradner WT. Cisplatin-induced emesis in the ferret: a new animal model. *Cancer Treat Rep* 1982;66:187-9.
- (11) Kris MG, Gralla RJ, Clark RA, Tyson LB, Fiore JJ, Kelsen DP, et al. Consecutive dose-finding trials adding lorazepam to the combination of metoclopramide plus dexamethasone: improved subjective effectiveness over the combination of diphenhydramine plus metoclopramide plus dexamethasone. *Cancer Treat Rep* 1985;69:1257-62.
- (12) Cunningham D, Dicato M, Verweij J, Crombez R, de Mulder P, du Bois A. Optimum anti-emetic therapy for cisplatin induced emesis over repeat courses: ondansetron plus dexamethasone compared with metoclopramide, dexamethasone plus lorazepam. *Ann Oncol* 1996;7:277-82.

## Notes

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M. G. Kris is a consultant to Pfizer, Inc., makers of CP-122,721, as well as to other pharmaceutical manufacturers; B. A. Pizzo holds stock in Pfizer, Inc.; and P. J. Hesketh has served as a consultant to Pfizer, Inc.

## An Explanation for the Increasing Incidence of Testis Cancer: Decreasing Age at First Full-Term Pregnancy

For unknown reasons, the incidence of cancer of the testis has increased substantially among white male populations of several European countries, the United States, Australia, and New Zealand (1). In Japan, the rates of testicular cancer have increased recently as well (2). An increase in the rate in white populations was first noted among men born after 1920, but this increase was not consistently sustained for men born between 1930 and 1945 (1). However, for men born in the 1950s onward, the increase in incidence has been uninterrupted. Explanations for this secular increase have been elusive. To some investigators, reports of a concomitant decrease in sperm counts in young men have suggested that an environmental exposure (e.g., pesticides and plant phytoestrogens) might be responsible (3).

A substantial body of experimental and epidemiologic evidence indicates that prenatal events or exposures are important risk factors for testis cancer (4). Excess maternal nausea and vomiting in the prenatal period, prenatal exogenous exposure to diethylstilbesterol (DES), and maternal obesity have been associated with increased risk of testis cancer and with the risk of cryptorchidism, which is by far the strongest known risk factor for testis cancer (5-7). These shared risk factors have suggested that in utero estrogen exposure might be a common cause of both cryptorchidism and cancer of the testis. Animal experiments have shown that estrogen treatment of pregnant mice can lead to undescended and hypogenetic testis (5). Similar abnormalities have been reported in male offspring of women exposed to DES and oral contraceptives during pregnancy (6).

The risk of testis cancer associated with excess nausea and vomiting is greatest for nausea requiring medical treatment (5). The strongest risk factors for such hyperemesis gravidarum are earlier age at pregnancy, nulliparity, and high body weight (8). Increased levels of bioavailable estradiol are found in the

**Table 1.** Age-specific and age-adjusted\* testis cancer incidence rates among non-Hispanic white males of Los Angeles County

| Year | Age, y        |               |               | All ages    |
|------|---------------|---------------|---------------|-------------|
|      | 20-24         | 25-29         | 30-34         |             |
| 1972 | 8.36          | 3.56          | 6.22          | 2.64        |
| 1973 | 5.44 (7.82)†  | 6.12 (7.68)   | 8.01 (7.67)   | 2.94 (3.25) |
| 1974 | 6.47          | 8.18          | 10.99         | 3.16        |
| 1975 | 11.01         | 12.81         | 5.44          | 4.25        |
| 1976 | 6.04          | 10.79         | 5.99          | 3.05        |
| 1977 | 10.64         | 14.43         | 10.70         | 4.36        |
| 1978 | 11.21 (9.18)  | 13.96 (13.78) | 12.37 (9.42)  | 4.62 (4.10) |
| 1979 | 8.20          | 12.44         | 9.34          | 3.69        |
| 1980 | 9.80          | 17.16         | 8.68          | 4.77        |
| 1981 | 11.15         | 15.65         | 14.30         | 4.66        |
| 1982 | 7.12          | 16.74         | 15.26         | 4.84        |
| 1983 | 10.73 (11.15) | 18.37 (16.69) | 17.87 (14.77) | 5.23 (5.09) |
| 1984 | 10.50         | 16.85         | 14.35         | 5.27        |
| 1985 | 16.27         | 15.85         | 12.00         | 5.44        |
| 1986 | 13.10         | 14.84         | 19.95         | 5.67        |
| 1987 | 8.40          | 16.48         | 20.26         | 6.22        |
| 1988 | 13.41 (10.68) | 13.87 (16.86) | 24.78 (20.99) | 6.16 (5.93) |
| 1989 | 8.36          | 22.47         | 22.94         | 5.94        |
| 1990 | 10.15         | 16.64         | 17.02         | 5.65        |
| 1991 | 12.09         | 11.85         | 17.85         | 5.44        |
| 1992 | 12.62 (10.80) | 12.97 (12.45) | 13.12 (13.59) | 5.20 (5.29) |
| 1993 | 10.73         | 11.93         | 13.98         | 5.23        |
| 1994 | 7.79          | 13.05         | 9.39          | 5.28        |

\*Adjusted to the 1970 U.S. population.

†Rates in parentheses = average annual rates over the indicated time line.

first trimester of pregnancy in women with hyperemesis gravidarum compared with control subjects and in the first trimester of a woman's first pregnancy compared with her second pregnancy (8,9).

The coincidence between the increasing incidence of testis cancer, particularly among men born since the 1950s, and decreasing age at first full-term pregnancy (FFTP) experienced by North American and presumably Western European women during the first half of this century (10) is striking. In the United States, the mean age at FFTP was 25.5 years for women born in 1910, but it fell more or less continuously to a nadir of less than 22 years for women born in 1940. It has since risen once again (10).

We propose that the three decades of continuous decline in maternal age at FFTP provides at least a partial explanation for the increase in testis cancer incidence among the corresponding male offspring birth cohorts of these women. Table 1 provides age-specific and age-adjusted incidence rates (AAIRs) of testis cancer for white males in Los Angeles County from 1972 through 1994. The AAIRs for testis cancer increase steadily, with a peak be-

tween 1987 and 1989 that is more than double the rate of the early 1970s, but subsequently decline by about 15% in the first half of the 1990s. Women who were born between 1910 and 1940 and experiencing a declining age at FFTP would have male offspring born approximately between 1930 and 1960 (10). These sons would be entering their peak ages (25-35 years) for testis cancer risk in the 1950s. By the early 1990s, men in the peak incidence ages for testis cancer would increasingly be those whose mothers sustained their FFTP after 1960, when age at FFTP was again on the rise.

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## References

- (1) Bergstrom R, Adami HO, Mohner M, Zatonski W, Storm H, Ekblom A, et al. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. *J Natl Cancer Inst* 1996;88:727-33.
- (2) Coleman MP, Esteve J, Damiacki P, Arslan A, Renard H. Trends in cancer incidence and mortality. *IARC Sci Publ* 1993;121:530-1.
- (3) Joffe M. Decreased fertility in Britain compared with Finland. *Lancet* 1996;347:1519-22.

- (4) Depue RH, Pike MC, Henderson BE. Estrogen exposure during gestation and the risk of testicular cancer. *J Natl Cancer Inst* 1983;71:1151-5.
- (5) Henderson BE, Benton B, Jing J, Yu MC, Pike MC. Risk factors for cancer of the testis in young men. *Int J Cancer* 1979;23:598-602.
- (6) Depue RH. Maternal and gestational factors affecting the risk of cryptorchidism and inguinal hernia. *Int J Epidemiol* 1984;13:311-8.
- (7) Morrison AS. Cryptorchidism, hernia, and cancer of the testis. *J Natl Cancer Inst* 1976;56:731-3.
- (8) Depue RH, Bernstein L, Ross RK, Judd HL, Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *Am J Obstet Gynecol* 1987;156:1137-41.
- (9) Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE. Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. *J Natl Cancer Inst* 1986;76:1035-9.
- (10) Gray GE, Henderson BE, Pike MC. Changing ratio of breast cancer incidence rates with age of black females compared with white females in the United States. *J Natl Cancer Inst* 1980;64:461-3.

## Notes

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## Re: Prospective Study of Sex Hormone Levels and Risk of Prostate Cancer

Gann et al. (1) reported that testosterone and sex hormone-binding globulin (SHBG) are independent and opposing risk factors for prostate cancer, while low circulating estradiol could be an additional risk factor. Their study has several advantages over those previously reported, in particular, measurement of hormones before cancer diagnosis and a much larger sample size [reviewed in (2)].

We have recently reported a population-based case-control study encompassing 93 patients with newly diagnosed, untreated prostate cancer and 98 control subjects. We found no clear association between testosterone, estradiol, and SHBG on the one hand and the risk of prostate cancer on the other (2). However, we evaluated each hormone without taking into consideration the possible mutual confounding effects—revealed subsequently in the study by Gann et al. (1)—that prompted us to re-analyze our data.

We found that the correlations between total testosterone and SHBG (Spearman  $r = .55$ ) and between total testosterone and estradiol ( $r = .29$ ) were virtually identical with those reported by Gann et al. (1) for their prospectively collected blood. Moreover, in our data, free testosterone (not analyzed in the study by Gann et al.) was also correlated with estradiol ( $r = .30$ ), but only weakly with SHBG ( $r = .13$ ). We further tried to disentangle possible independent effects of testosterone, estradiol, and SHBG by mutual adjustment; for comparison we also show data without such adjustment (Table 1).

Associations between mutually adjusted testosterone and SHBG and risk for prostate cancer are weaker than in the study by Gann et al., and the confidence intervals are wide. The risk estimates from univariate analyses of estradiol and SHBG and prostate cancer in our study did not appear to be confounded by testosterone, since odds ratios and  $P$  values for trend are largely unaffected by mutual adjustment.

In agreement with the results of Gann et al., effects of testosterone and estradiol on prostate cancer seem to be more pronounced in older men. In our study, the weaker effect of SHBG could be due to the fact that our study subjects were 8 years older on average (mean age, 70 years versus 62 years in the study by Gann et al.); in fact, our estimates for SHBG are compatible with their esti-

mates in the subgroup of men 62 years of age and older.

It appears that patterns in associations of testosterone, estradiol, and SHBG with prostate cancer in our case-control study are in general compatible with those observed by Gann et al. in their prospective investigation and point to a complex but biologically meaningful interplay of hormones in the etiology of prostate cancer.

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## References

- (1) Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996;88:1118-26.
- (2) Andersson SO, Adami HO, Bergstrom R, Wide L. Serum pituitary and sex steroid hormone levels in the etiology of prostatic cancer—a population-based case-control study. *Br J Cancer* 1993;68:97-102.

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**Table 1.** Risk for prostate cancer by tertile of plasma level of total testosterone (T), free testosterone (TF), estradiol (E<sub>2</sub>), and sex hormone-binding globulin (SHBG)\*

| Hormones adjusted for                      | OR by tertile |           |       | 95% CI for 3rd tertile | P for trend |
|--|---------------|-----------|-------|------------------------|-------------|
|  | 1             | 2         | 3     |                        |             |
| Total testosterone (T), ng/mg              | <3.50         | 3.50-5.07 | >5.07 |                        |             |
| Age, y                                     | 1.0           | 1.18      | 0.97  | 0.49-1.94              | .93         |
| Age, E <sub>2</sub> , and SHBG             | 1.0           | 1.23      | 1.27  | 0.55-2.93              | .55         |
| Age, E <sub>2</sub> , and SHBG (men ≥70 y) | 1.0           | 2.28      | 1.81  | 0.62-5.28              | .25         |
| TF, pg/mL                                  | <70.0         | 70.0-94.2 | >94.2 |                        |             |
| Age, y                                     | 1.0           | 1.51      | 1.21  | 0.60-2.42              | .59         |
| Age, E <sub>2</sub> , and SHBG             | 1.0           | 1.51      | 1.46  | 0.69-3.08              | .30         |
| Age, E <sub>2</sub> , and SHBG (men ≥70 y) | 1.0           | 1.40      | 1.71  | 0.63-4.62              | .29         |
| E <sub>2</sub> , pg/mL                     | <11.6         | 11.6-23.0 | >23.0 |                        |             |
| Age, y                                     | 1.0           | 0.85      | 0.62  | 0.30-1.25              | .18         |
| Age, TF, and SHBG                          | 1.0           | 0.84      | 0.60  | 0.28-1.30              | .15         |
| Age, TF, and SHBG (men ≥70 y)              | 1.0           | 0.59      | 0.49  | 0.18-1.35              | .16         |
| SHBG, nmol/L                               | <40.3         | 40.3-59.7 | >59.7 |                        |             |
| Age, y                                     | 1.0           | 0.90      | 0.76  | 0.37-1.56              | .46         |
| Age, T, and E <sub>2</sub>                 | 1.0           | 0.84      | 0.75  | 0.32-1.77              | .47         |
| Age, T, and E <sub>2</sub> (men ≥70 y)     | 1.0           | 0.85      | 0.76  | 0.25-2.46              | .59         |

\*Odds ratios (ORs), with 95% confidence intervals (CIs) for the highest compared with the lowest tertile, obtained through logistic regression.

## Re: Involuntary Smoking and Lung Cancer: a Case-Control Study

Reviews regarding the relationship of environmental tobacco smoke (ETS) to

lung cancer risk in nonsmokers depend greatly on published data from individual studies. We recently became aware of errors in the 95% confidence limits in an article by Garfinkel et al. published in the Journal (1).

In that article, an inappropriate value of the  $z$ -statistic (the odds ratio [OR]

rather than 1.96) was used in the calculation of the confidence limits in Tables 4, 5, and 7. Correct confidence limits can be calculated by using the cell counts. Cell counts are not given for Tables 3 and 6, but an analysis of the ratios of upper to lower confidence limits indicates that the confidence limits in

**Table 1.** Tables 4, 5, and 7 from Garfinkel et al. (1) with corrected confidence limits\*

Table 4. Number of cases and controls exposed to smoke of others during 5 and 25 years before diagnosis

| Variable                     | Exposure No. of hr/day |           |           |           | Total     |
|------------------------------|------------------------|-----------|-----------|-----------|-----------|
|                              | None                   | 1-2       | 3-6       | $\geq 7$  |           |
| Last 5 years                 |                        |           |           |           |           |
| No. of cases                 | 80                     | 15        | 25        | 14        | 54        |
| No. of controls              | 263                    | 31        | 59        | 49        | 139       |
| Odds ratio (OR)              | 1.00                   | 1.59      | 1.39      | 0.94      | 1.28      |
| 95% confidence interval (CI) | —                      | 0.82-3.09 | 0.82-2.37 | 0.49-1.79 | 0.85-1.91 |
| Last 25 years                |                        |           |           |           |           |
| No. of cases                 | 42                     | 17        | 45        | 30        | 92        |
| No. of controls              | 136                    | 72        | 109       | 85        | 266       |
| OR                           | 1.00                   | 0.77      | 1.34      | 1.14      | 1.12      |
| 95% CI                       | —                      | 0.41-1.44 | 0.82-2.18 | 0.67-1.96 | 0.74-1.70 |

Table 5. Smoke exposure before lung cancer diagnosis, as classified by husband's smoking habits

| Variable                         | Husband's total smoking habits |                |           |           |                   | All types of smoking |
|----------------------------------|--------------------------------|----------------|-----------|-----------|-------------------|----------------------|
|                                  | None                           | Cigarettes/day |           |           | Cigar and/or pipe |                      |
|                                  |                                | <20            | 20-39     | $\geq 40$ |                   |                      |
| No. of cases                     | 43                             | 11             | 32        | 30        | 18                | 91                   |
| No. of controls                  | 148                            | 45             | 102       | 52        | 55                | 254                  |
| OR                               | 1.00                           | 0.84           | 1.08      | 1.99      | 1.13              | 1.23                 |
| 95% CI                           | —                              | 0.40-1.77      | 0.64-1.82 | 1.13-3.49 | 0.60-2.12         | 0.81-1.87            |
| Husband's smoking habits at home |                                |                |           |           |                   |                      |
| Variable                         | None                           | Cigarettes/day |           |           | Cigar and/or pipe | All types of smoking |
|                                  |                                | <10            | 10-19     | $\geq 20$ |                   |                      |
| No. of cases                     | 44                             | 29             | 17        | 26        | 18                | 90                   |
| No. of controls                  | 157                            | 90             | 56        | 44        | 55                | 245                  |
| OR                               | 1.00                           | 1.15           | 1.08      | 2.11      | 1.17              | 1.31                 |
| 95% CI                           | —                              | 0.67-1.96      | 0.57-2.05 | 1.17-3.80 | 0.62-2.19         | 0.87-1.98            |

Table 7. Number of cases and controls exposed to smoke of others at home, at work, and in other areas

| Variable        | Smoke exposure |           |           |                |
|-----------------|----------------|-----------|-----------|----------------|
|                 | None           | At home   | At work   | In other areas |
| Last 5 years    |                |           |           |                |
| No. of cases    | 80             | 37        | 14        | 13             |
| No. of controls | 262            | 99        | 52        | 24             |
| OR              | 1.00           | 1.22      | 0.88      | 1.77           |
| 95% CI          | —              | 0.78-1.93 | 0.46-1.67 | 0.86-3.64      |
| Last 25 years   |                |           |           |                |
| No. of cases    | 42             | 73        | 34        | 19             |
| No. of controls | 135            | 204       | 118       | 43             |
| OR              | 1.00           | 1.15      | 0.93      | 1.42           |
| 95% CI          | —              | 0.74-1.78 | 0.55-1.55 | 0.75-2.70      |

\*Some columns and footnotes have been omitted.

those two tables probably suffer from the same error.

Since most of the ORs in Tables 4, 5, and 7 are less than the standard  $z$ -value, 1.96, most of the published confidence limits are overly narrow. This is particularly true when the OR is close to or below the null. The published ORs are correct, but meta-analyses that include this study should use the cell counts to calculate the standard error and appropriate weight for each OR instead of using the confidence limits. Otherwise, most of the results in this study will be weighted too heavily.

The US Environmental Protection Agency meta-analysis of ETS and lung cancer (2) included the estimated ORs of lung cancer from spousal ETS from this study. The appropriate ORs and confidence limits were used. However,

at least one meta-analysis (3) of lung cancer and workplace exposure to ETS appears to have used the published confidence limits in Table 7 to calculate weights. Since the two workplace ORs (0.88 and 0.93) are less than the null, weights calculated from the published confidence limits are heavily overweighted by a factor of about five.

For the reader's convenience, corrected Tables 4, 5, and 7 are shown in Table 1.

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## References

- (1) Garfinkel L, Auerbach O, Joubert L. Involuntary smoking and lung cancer: a case-control study. *J Natl Cancer Inst* 1985;75:463-9.

- (2) US Department of Health and Human Services. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders: The Report of the U.S. Environmental Protection Agency. U.S. Department of Health and Human Services, Public Health Services, National Institutes of Health and US Environmental Protection Agency, Office of Research and Development, Office of Air and Radiation. NIH Publ No. 93-3605, 1993: 125.

- (3) Chappell WR, Gratt LB. A graphical method for pooling epidemiological studies [letter]. *Am J Public Health* 1996;86:748-50.

## Notes

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