Alcohol consumption and risk of benign proliferative epithelial disorders of the breast: a case–cohort study

Thomas E Rohan*, Meera Jain and Anthony B Miller
Department of Public Health Sciences, University of Toronto, Toronto, Canada

Submitted 3 February 1998: Accepted 9 July 1998

Abstract

Objective: To study the association between alcohol consumption and risk of benign proliferative epithelial disorders (BPED) of the breast (conditions which are thought to have premalignant potential).
Design: Case–cohort study.
Setting: The study was undertaken within the 56,537 women in the Canadian National Breast Screening Study (NBSS) who completed self-administered dietary questionnaires. (The NBSS is a randomized controlled trial of screening for breast cancer in women aged 40–59 years at recruitment.)
Subjects: The study subjects were the 657 women in the dietary cohort who were diagnosed with biopsy-confirmed incident BPED. For comparative purposes, a subcohort consisting of a random sample of 5681 women was selected from the full dietary cohort. After exclusions for various reasons, the analyses were based on 557 cases and 5028 non-cases.
Results: When compared to non-drinkers, rate ratios (95% CI) for those consuming >0 and ≤ 10 g of ethanol day^{-1}, >10 and ≤ 20 g day^{-1}, >20 and ≤ 30 g day^{-1} and >30 g day^{-1} were 0.35 (0.27–0.45), 0.26 (0.18–0.39), 0.29 (0.18–0.48), and 0.23 (0.13–0.40), respectively (the associated P value for the trend was 0.089). Similar findings were obtained from analyses conducted separately in the screened and control arms of the NBSS, in premenopausal and postmenopausal women, and for non-atypical and atypical forms of BPED, and there was little difference between the results for screen-detected and interval-detected BPED.
Conclusions: Alcohol consumption was associated with a non-dose-dependent reduction in risk of BPED.

Keywords
Alcohol
Benign breast disease
Breast cancer

There is some evidence for a positive association between alcohol consumption and risk of breast cancer[1], and it has been suggested that the association might be causal[2]. However, the stage of the carcinogenic process at which alcohol might exert such an effect is not known. In broad terms, there are two possibilities: either alcohol might act at a relatively early stage, by influencing the risk of developing lesions with premalignant potential, or it might act at a later stage by influencing the risk of progression of such lesions to breast cancer. The former of these possibilities was addressed in the case–cohort study reported here, in which the association between alcohol consumption and risk of benign proliferative epithelial disorders (BPED) of the breast was examined. BPED of the breast are associated with increased risk of breast cancer[3], and recent experimental evidence supports the notion that they might be precursors of breast cancer[4].

Materials and methods

Overview

The study population and methods (including the procedures for follow-up and case identification) have been described in detail elsewhere[5]. In brief, the investigation was conducted as a case–cohort study within the cohort of 56,837 women in the Canadian National Breast Screening Study (NBSS) who completed a self-administered quantitative food frequency questionnaire (in addition to an epidemiological questionnaire, which was completed by all NBSS participants). The NBSS is a multicentre randomized controlled trial of (primarily) mammographic screening for breast cancer in 89,835 women aged 40–59 years at recruitment[6,7]. Participants were recruited between 1980 and 1985 by various means, including personal invitation by letter, group mailings to employees of large institutions and to members of professional associations, advertisements in newspapers, and public service announcements on radio and television.

Dietary and risk factor data

On enrolment in the NBSS, all participants completed a questionnaire which sought identifying information, as

*Corresponding author: E-mail tom.rohan@utoronto.ca

https://doi.org/10.1079/PHN19980023 Published online by Cambridge University Press

well as data on factors such as demographic characteristics, family history of breast cancer, menstrual and reproductive history, use of oral contraceptives and replacement oestrogens, and cigarette smoking. Starting in 1982, a self-administered quantitative food frequency questionnaire was distributed to all new attendees at all screening centres, and to women returning to the screening centres for rescreening. (By the time that the dietary questionnaire was introduced, some women who had already been enroled in the study were not seen again at the screening centres.) A total of 56,837 women returned completed dietary questionnaires, and these women constitute the cohort on which the study described here was based.

The food frequency questionnaire contained questions on the frequency of consumption and usual portion size of 86 food items, including consumption of beer (in units of 12 oz – 340 g – cans or bottles), wine (4 oz – 113 g – glass) and spirits (1.5 oz – 42.5 g – measure), and it also had an open-ended section for the description of other food items normally eaten. Photographs of various portion sizes were included in the questionnaire to assist participants with quantification of intake. Data from the self-administered questionnaire were used to estimate daily intake of beer, wine and spirits, as well as that of calories, and of various macro- and micronutrients, using a nutrient database developed by modifying and extending food composition tables from the United States Department of Agriculture to include typically Canadian foods[8].

Case definition

Cases were women who were diagnosed during the active follow-up phase of the study (which ended in 1988) with incident screen- or interval-detected BPED of the breast confirmed by biopsy. Screen-detected cases were those which were detected at one of the scheduled screening visits (excluding the first), while interval-detected cases were those which were detected between scheduled visits. In all, 657 cases were identified, of whom 62 were in the subcohort (see below). Of these 657 women, 97 were excluded from the present study because their dietary questionnaires were not available. Women who developed breast cancer during the NBSS prior to the development of BPED were excluded from consideration as cases.

Histopathology

In the NBSS, histological sections were classified according to the classification scheme employed by Page, which has been described in detail elsewhere[9]. Briefly, use of this scheme entails making an assessment of the presence or absence of epithelial proliferation, and, when epithelial proliferation is deemed to be present, classifying the lesions further according to the presence or absence of histological atypia (atypical lesions have some but not all of the features of carcinoma *in situ*). Diagnoses were made by local pathologists in each study area. Each diagnosis was reviewed for study purposes by a local reference pathologist, and classified using agreed criteria. If there was disagreement between the local and reference pathologists, the slides were submitted for NBSS panel review. Diagnoses made by the reference pathologists were used in the present study (since not all biopsies were subjected to panel review).

Construction of the subcohort

The subcohort was constructed by selecting a stratified (by recruitment centre) random sample of 5681 women from the dietary cohort. Of those selected, the 173 who did not return any of the follow-up questionnaires were excluded from the present analysis, as were the 375 women whose dietary questionnaires were not available. (Of those lost to follow-up 39 also did not have dietary questionnaires available.)

Statistical analysis

Analyses were conducted for alcohol from all sources combined, and for alcohol from beer, wine and spirits separately. For these analyses, the basic unit of alcohol exposure was grams of ethanol consumed per day (categorized for some analyses). Standard servings of beer, wine and spirits were estimated to contain 13.2 g, 10.8 g and 22.6 g of ethanol, respectively[10].

Incidence rate ratios for the association between alcohol consumption and risk of BPED were estimated using Poisson regression, and robust standard errors were calculated using the information sandwich[11], thereby yielding the appropriate confidence intervals for the rate ratios given the case–cohort sampling. Cases contributed person-time to the study from their date of enrolment until the date of diagnosis of their BPED, and non-cases contributed person-time from their date of enrolment until the last date on which they returned a follow-up questionnaire indicating that they had not had BPED. (The median follow-up time was approximately 4 years.) The incidence rate ratios were adjusted for energy intake (fitted as a continuous variable) and for potential confounding by the following non-dietary variables: age, family history of breast cancer, practice of breast self-examination, menopausal status, number of pregnancies and body mass index (weight/height^2), as well as randomization group and study centre. Tests for trend (on one degree of freedom) in the association between (non-zero levels of) alcohol consumption and risk of BPED were performed by fitting categorized variables as continuous variables in the Poisson regression models. Tests for interaction (e.g. between alcohol consumption and treatment arm) were based on

likelihood ratio tests comparing models with and without product terms representing the variables of interest. The likelihood ratio test that all of the interaction parameters were zero was performed by referring the differences between the deviances of models with and without interaction terms to the chi-squared distribution on degrees of freedom equal to the number of interaction parameters.

As indicated previously[5], those subjects for whom the estimate of $\log_e$-transformed total energy intake was more than 3 SDs from the mean $\log_e$-transformed total energy intake were excluded from further consideration, since their estimated energy intake was highly suggestive of incorrectly recorded intake. This resulted in the exclusion of 46 subjects (three cases, none of whom were in the subcohort, and 43 non-cases). Therefore, given the various exclusions described above, the main analyses were based on 557 cases (657 minus 97 with no diet questionnaires and minus 3 with extreme values for energy intake) and 5028 non-cases (5681 in subcohort minus 173 with no follow-up, minus 375 with no diet questionnaires, minus 43 with extreme values for energy intake and minus 62 incident cases in subcohort).

Results

Table 1 shows the relationship between alcohol consumption and potential confounders of its association with risk of BPED – the numbers in the body of the table are the percentages of non-cases with a given attribute at various levels of alcohol consumption. There were positive associations between alcohol consumption and years of education, premenopausal status, ever use of oral contraceptives, ever use of cigarettes and energy intake; and inverse associations between alcohol consumption and age at menarche and Quetelet's index. Patterns for the other variables shown in the table were less clear, but there was some suggestion that drinkers were younger than non-drinkers, and were more likely to have a family history of breast cancer, to have practised breast self-examination and to have a relatively low fibre intake. Of the variables shown in Table 1, age, number of pregnancies and Quetelet's index had inverse associations with risk of BPED; premenopausal status, family history of breast cancer and practice of breast self-examination were associated with increased risk; and the remaining variables were associated with little alteration in risk.

A substantially smaller proportion of cases (41.7%) than non-cases (60.7%) reported that they consumed alcohol (irrespective of type), and the mean total alcohol intake of cases who reported any consumption (10.4 g day^{-1}, SD 13.3 g day^{-1}) was lower than that in non-cases who reported drinking alcohol (12.0 g day^{-1}, SD 18.2 g day^{-1}). (An intake of 10 g day^{-1} corresponds approximately to one glass of wine, one-half serving of spirits, and slightly less than one bottle or can of beer per day.) The adjusted incidence rate ratio (95% CI) for drinkers versus non-drinkers of alcohol was 0.31 (0.25–0.40). Table 2 shows that there was a 65–80% reduction in risk at all non-zero levels of alcohol intake, and that in drinkers, there was relatively little variation in risk with intake. In drinkers, the change in risk per 10 g increase in total alcohol intake per day was 0.90 (95% CI, 0.79–1.01).

The adjusted incidence rate ratios for those who reported consumption of beer, wine and spirits versus that for those who reported that they did not consume

Table 1 Relationship between alcohol consumption and potential confounders in the non-cases

Attribute	Per cent with attribute and alcohol intake of		
	0 g day^{-1} (n = 1978)	> 0 & < 20 g day^{-1} (n = 2486)	≥ 20 g day^{-1} (n = 564)
Age (55–59 years)	20.7*	17.9	19.3
≥ 16 years of education	15.7	17.8	25.9
Age at menarche ≤ 11 years	18.2	16.1	14.8
Never pregnant	12.7	11.8	12.4
Nulliparous	15.4	13.7	16.1
Premenopausal	44.5	48.4	50.7
Positive family history of breast cancer	11.6	10.3	13.1
Ever practised breast self-examination	50.6	53.2	52.2
Ever used oral contraceptives	56.1	62.8	69.2
Ever smoked cigarettes	45.5	48.7	68.0
Quetelet's index > 28.4 kg m^{-2} †‡	25.1	17.8	12.5
Energy intake > 2474.7 kcal day^{-1}‡	19.3	20.0	22.7
Fat intake > 120.4 g day^{-1}‡	20.1	20.3	18.3
Fibre intake < 11.8 g day^{-1}‡	23.9	17.2	27.7
β-carotene intake < 3150.8 IU day^{-1}‡	23.2	17.5	20.0

*Percentage.
†Quetelet's index = weight (kg)/height(m)^2.
‡Highest quintile level for Quetelet's index, and energy and fat intake; lowest quintile level for fibre and β-carotene intake.

https://doi.org/10.1079/PHN19980023 Published online by Cambridge University Press

Table 2 Association between daily total alcohol consumption and risk of benign proliferative epithelial disorders of the breast*

Level (g day^{-1})	No. cases	Estimated person-years of follow-up	Incidence rate ratio	95% CI
0	325	69,357	1†	
>0 & <10	154	68,770	0.35	0.27–0.45
≥10 & <20	39	19,361	0.26	0.18–0.39
≥20 & <30	23	10,242	0.29	0.18–0.48
≥30	16	9776	0.23	0.13–0.40
P (trend)			0.089	

*Adjusted for age, family history of breast cancer, practice of breast self-examination, menopausal status, number of pregnancies, Quetelet's index, study allocation, study centre and energy intake.
†Reference category.

the corresponding beverage were 0.55 (0.42–0.72), 0.41 (0.33–0.51) and 0.40 (0.32–0.49), respectively. The associations for these beverages are examined by level of consumption in Table 3, which displays incidence rate ratios derived from a model in which terms representing each of the alcoholic beverages were included simultaneously, to enable examination of the effect of equivalent amounts of alcohol from each beverage. For these analyses, drinkers were categorized into two levels of alcohol consumption, due to the relatively small numbers of individuals who reported that they consumed these beverages. Risk was decreased at non-zero levels of intake for all beverages, but particularly for consumption of wine and spirits.

The results shown in Tables 2 and 3 were essentially the same after additional adjustment for age at menarche, age at first live birth, cigarette smoking, use of oral contraceptives and years of education (included simultaneously), and also after additional adjustment (separately) for fat, fibre, and β-carotene intake. They were also similar after exclusion of the 155 cases and 779 non-cases with a history of breast disease (not breast cancer), and after exclusion of the 34 cases whose diagnosis was made within 6 months of recruitment, and whose reported alcohol intake might therefore have been influenced by the early symptoms of their breast disease.

As indicated earlier, risk of BPED decreased with increasing age. Therefore, the Poisson regression analyses were repeated after subdividing the follow-up experience of each individual into that accrued within 5-year age bands (starting at age 40 years), and then entering a term for age band into the models. In this way, BPED rates were allowed to vary with age (although rates were assumed to be constant within each age band). The results of these analyses were very similar to those shown in Tables 2 and 3. For example, the incidence rate ratios and 95% CI for the second to fifth levels of total alcohol intake relative to the rate for non-drinkers were 0.33 (0.25–0.44), 0.24 (0.16–0.37), 0.30 (0.18–0.50) and 0.23 (0.13–0.42), respectively.

Given that the present study was conducted within a randomized controlled trial of screening for breast cancer, it seemed likely that there would be a greater likelihood of detection of BPED in the screened group than in the control group. Indeed, the screened group contained 401 cases (and 2510 non-cases), and the control group contained 156 cases (and 2518 non-cases). It was of interest, therefore, to examine the association between alcohol and BPED in the two

Table 3 Association between daily consumption of alcohol from beer, wine and spirits, and risk of benign proliferative epithelial disorders (BPED) of the breast*

Beverage	Level (g day^{-1})	No. cases	Estimated person-years of follow-up	Incidence rate ratio	95% CI
Beer†	0	480	141,182	1‡	
	>0 & <10	69	33,481	0.84	0.63–1.12
	≥10	8	2844	0.76	0.35–1.65
Wine†	0	342	83,064	1‡	
	>0 & <10	191	81,275	0.59	0.46–0.74
	≥10	24	13,168	0.41	0.26–0.66
Spirits†	0	416	105,252	1‡	
	>0 & <10	111	55,290	0.55	0.43–0.71
	≥10	30	16,963	0.46	0.31–0.71

*Adjusted for age, family history of breast cancer, practice of breast self-examination, menopausal status, number of pregnancies, Quetelet's index, study allocation, study centre and energy intake.
†Included simultaneously in regression model.
‡Reference category.

https://doi.org/10.1079/PHN19980023 Published online by Cambridge University Press

Table 4 Association between daily total alcohol consumption and risk of non-atypical and atypical forms of benign proliferative epithelial disorders (BPED) of the breast*

BPED type	Level (g day^{-1})	No. cases	Estimated person-years of follow-up	Incidence rate ratio	95% CI
Non-atypical	0	288	69,270	1†	
	>0 & <10	143	68,750	0.37	0.28–0.48
	≥10	67	39,354	0.27	0.19–0.37
Atypical	0	37	68,726	1†	
	>0 & <10	11	68,476	0.19	0.09–0.40
	≥10	11	39,244	0.24	0.11–0.54

*Adjusted for age, family history of breast cancer, practice of breast self-examination, menopausal status, number of pregnancies, Quetelet's index, study allocation, study centre and energy intake.
†Reference category.

Table 5 Association between daily total alcohol consumption and risk of benign proliferative epithelial disorders of the breast by menopausal status*

Menopausal category	Level (g day^{-1})	No. cases	Estimated person-years of follow-up	Incidence rate ratio	95% CI
Premenopausal	0	179	31,451	1†	
	>0 & <10	89	33,162	0.35	0.25–0.50
	≥10	49	20,357	0.26	0.17–0.40
Postmenopausal	0	88	27,135	1†	
	>0 & <10	40	25,370	0.34	0.21–0.54
	≥10	15	13,215	0.21	0.11–0.39

*Perimenopausal women are not included in this table. Rate ratios are adjusted for age, family history of breast cancer, practice of breast self-examination, menopausal status, number of pregnancies, Quetelet's index, study allocation, study centre and energy intake.
†Reference category.

groups separately. For the most part, the results for the two groups were similar, and differed little from those shown in Tables 2 and 3. For example, in the screened group, the incidence rate ratios and 95% CI for the second to fifth levels of daily total alcohol intake relative to the rate for non-drinkers were 0.36 (0.27–0.49), 0.26 (0.16–0.41), 0.34 (0.20–0.59) and 0.22 (0.11–0.42), respectively; in the control group, the corresponding estimates were 0.30 (0.18–0.48), 0.26 (0.12–0.54), 0.17 (0.06–0.52) and 0.24 (0.09-0.65), respectively. Furthermore, on formal testing, there were no statistically significant between-group differences ($\chi^2(4) = 0.202$, $P = 0.995$). (Similar findings were obtained when the analyses were repeated after further subdivision of the study population into those aged 40–49 years and 50–59 years (data not shown).)

Cases of BPED were detected either at a scheduled visit to a screening centre, or by the study participants or their physicians between visits. It is conceivable that there are aetiological differences between the two types of BPED. In particular, the screen-detected cases might be less extensive and develop more slowly than interval-detected cases. However, separate analyses for screen- and interval-detected BPED revealed that the results for the two types of BPED were mostly similar to those observed overall (data not shown).

Table 4 shows the association between total alcohol consumption and risk of non-atypical and atypical forms of BPED, and Table 5 shows the association between alcohol and risk of BPED in premenopausal and postmenopausal women (using menopausal status at recruitment). In general, the results were similar for the two types of BPED, and for the two menopausal strata, and they differed little from those shown in Table 2. (For these analyses, drinkers were categorized into two levels of alcohol consumption due to the relatively small numbers of individuals at the higher levels of intake.) When the analyses within menopausal strata were repeated using menopausal status at diagnosis, the results were similar to those shown in Table 5, although the reduction in risk in premenopausal women was less pronounced (data not shown). Results for the individual beverages were mostly similar to those shown in Table 3 (data not shown), although the point estimates for beer were relatively unstable, reflecting the small number of cases at the uppermost level of intake.

Finally, there was no evidence for interactions between alcohol consumption and menopausal status ($\chi^2(6) = 0.9958$, $P = 0.986$), cigarette smoking ($\chi^2(4) = 0.6873$, $P = 0.953$) or intake of fat ($\chi^2(16) = 2.323$, $P > 0.999$), fibre ($\chi^2(16) = 2.2973$, $P > 0.99$) or β-carotene ($\chi^2(16) = 2.7756$, $P > 0.99$).

Discussion

Overall, the results of the present study suggest that alcohol consumption is associated with reduced risk

https://doi.org/10.1079/PHN19980023 Published online by Cambridge University Press

of BPED. The reduction in risk, which was not dose-dependent, was observed for alcohol from all sources combined, and for alcohol from beer, wine and spirits separately (particularly wine and spirits). The latter finding suggests that the reduction in risk is related to alcohol *per se* rather than alcohol from a specific source. These findings were much the same when analyses were conducted separately in the screened and control arms of the NBSS, in premenopausal and postmenopausal women, and for non-atypical and atypical forms of BPED, and there was little difference between the results for screen-detected and interval-detected BPED.

The precise mechanisms by which alcohol might influence the risk of benign breast disease (and breast cancer) have not been elucidated. However, there are numerous possibilities, including induction of disturbances in nutrient[13] and endocrine status[13,14], exposure of target tissues to carcinogenic contaminants in alcohol, enhancement of the metabolic activation of compounds into carcinogens and inhibition of their detoxification, and suppression of immune function[15]. In the context of these mechanisms, from which it might be predicted that alcohol consumption would be associated with increased risk of BPED, the reduction in risk observed in the present study was contrary to expectation.

Chance and confounding seem relatively unlikely to account for the present findings since the study was large and had ample power to detect small effects (at least for all subjects combined, and at the relatively moderate levels of intake observed here), and the estimates of association were adjusted for a wide range of potential confounders. In contrast, bias could have arisen from several sources, as discussed in detail elsewhere[5]. In brief, the possibility of selection bias arising from the fact that unknown proportions of women with benign breast disease come to clinical attention and proceed to biopsy was largely mitigated in the present study, since the participants were screened (to a variable extent) for breast disease. Furthermore, as indicated above, when the analyses were conducted separately in the screened and control arms of the NBSS (thereby restricting attention in each case to individuals screened to a comparable extent), the results were largely the same as those observed overall. Selection bias arising from the fact that dietary questionnaires were not located for all subjects (resulting in the exclusion of some) is also relatively unlikely, given that there was little difference between those with and without located dietary information with respect to a wide range of variables related to the aetiology and detection of benign breast disease. Selection bias from loss to follow-up also seems relatively unlikely, although some anti-conservative bias cannot be ruled out, since a slightly smaller proportion of those lost to follow-up than those not lost were drinkers (52.6 versus 58.8%, respectively; $\chi^2(4) = 8.62$, $P = 0.071$). Bias might have arisen due to misclassification of the study subjects with respect to exposure and/or disease status. With respect to disease status, it is possible that some non-cases had undetected BPED, and that some of the cases were incorrectly classified as having BPED, the result of which would have been to bias estimates of association conservatively. With respect to the quantification of alcohol intake, it should be assumed that the intrinsic limitations of food frequency questionnaires lead to some individuals being misclassified with respect to intake, which generally will result in attenuation of true associations[16]. Indeed, since the measure of alcohol intake used in this study related to recent consumption (prior to recruitment), the reference group of non-drinkers might have included some ex-drinkers, and it is conceivable that their risk of BPED might differ from that of non-drinkers. Furthermore, it was not possible to examine risk in association with lifetime consumption. Recall bias is not an issue here since the study was prospective.

There appears to have been only one previous study of the association between alcohol consumption and risk of BPED[17]. In that investigation, a case–control study conducted in Australia, alcohol consumption was not associated with altered risk, either overall, or when current and ex-drinkers were examined separately. However, the study employed both community and 'biopsy' controls (subjects whose breast biopsy did not show evidence of BPED). The former might have been inappropriate since the case series was not necessarily representative of all cases[18], while use of the latter might have resulted in overmatching[19]. These potential sources of bias were not present in the study reported here.

In conclusion, the results of the present study suggest that alcohol consumption is associated with reduced risk of BPED of the breast. This finding is not necessarily inconsistent with the positive association which has been observed between alcohol consumption and risk of breast cancer (indeed, there was a weak positive association between alcohol and breast cancer in a previous case–control analysis in the NBSS cohort[10], in which the adjusted relative risk for those consuming at least 30 g of alcohol per day was 1.22 (0.78–1.90)), in the light of which it might be postulated that alcohol also acts after the development of BPED by stimulating their progression to breast cancer. This hypothesis requires confirmation in studies of the association between alcohol consumption and risk of breast cancer in women with BPED of the breast, and if substantiated, it raises the possibility that interventions to reduce alcohol consumption in women with BPED might reduce the risk of subsequent breast cancer.

Acknowledgements

We thank Mr Andrew White for preparing the data file for statistical analysis, and we also thank the reviewers for their helpful comments.

References

1 Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes Control* 1994; **5**: 73–82.
2 Hunter DJ, Willett WC. Nutrition and breast cancer. *Cancer Causes Control* 1996; **7**: 56–68.
3 Bodian CA. Benign breast diseases, carcinoma *in situ*, and breast cancer risk. *Epidemiol. Rev.* 1993; **15**: 177–87.
4 Miller FR, Soule HD, Tait L, *et al.* Xenograft model of progressive human proliferative breast disease. *J. Natl Cancer Inst.* 1993; **85**: 1725–32.
5 Rohan TE, Jain M, Miller AB. A case–cohort study of diet and risk of benign proliferative epithelial disorders of the breast (Canada). *Cancer Causes Control* 1998; **9**: 19–27.
6 Miller AB, Howe GR, Wall C. The national study of breast cancer screening: protocol for a Canadian randomized controlled trial of screening for breast cancer in women. *Clin. Invest. Med.* 1981; **4**: 227–58.
7 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study. I. Breast cancer detection and death rates among women aged 40 to 49 years. II. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992; **147**: 1459–88.
8 Morgan RW, Jain M, Miller AB, *et al.* A comparison of dietary methods in epidemiologic studies. *Am. J. Epidemiol.* 1978; **107**: 488–98.
9 Page DL, Anderson TJ. *Diagnostic Histopathology of the Breast.* Edinburgh: Churchill Livingstone, 1987.
10 Friedenreich CM, Howe GR, Miller AB, Jain MG. A cohort study of alcohol consumption and risk of breast cancer. *Am. J. Epidemiol.* 1993; **137**: 512–20.
11 Huber PJ. The behaviour of maximum likelihood estimates under non-standard conditions. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*, vol. 1. Berkeley: University of California Press, 1967, 221–33.
12 Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat. Med.* 1989; **8**: 1051–69.
13 Hillers VN, Massey LK. Interrelationships of moderate and high alcohol consumption with diet and health status. *Am. J. Clin. Nutr.* 1985; **41**: 356–62.
14 Williams RR. Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin, TSH, and MSH. *Lancet* 1976; **i**: 996–9.
15 Reichman ME, Judd JT, Longcope C, *et al.* Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J. Natl Cancer Inst.* 1993; **85**: 722–7.
16 Blot WJ. Alcohol and cancer. *Cancer Res.* 1992; **52** (suppl.): 2119–23.
17 Rohan TE, Cook MG. Alcohol consumption and risk of benign proliferative epithelial disorders of the breast in women. *Int. J. Cancer* 1989; **43**: 631–6.
18 Berkowitz GS, Canny PF, Vivolsi VA, Merino MJ, O'Connor TZ, Kelsey JL. Cigarette smoking and benign breast disease. *J. Epidemiol. Comm. Health 1985;* **39**: 308–13.
19 Vessey MP. Comment. *J. Chron. Dis.* 1979; **32**: 64–6.