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Alcohol and Breast Cancer: Update from an Italian Case-control Study

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Abstract—*The analysis of alcohol and breast cancer risk from an Italian case-control study of breast cancer has been updated to include a total of* 2402 *women with histologically confirmed breast cancer and* 2220 *controls with acute conditions unrelated to any of the established or potential risk factors for breast cancer, admitted to a network of teaching and general hospitals in the greater Milan area. Compared with non-drinkers, the estimated relative risk for ever drinkers was* 1.4 (95% *CI* = 1.2–1.6). *The multivariate risks were* 1.3 *for less than* 1 *drink* (*e.g.* 10 *g of ethanol*) *per day,* 1.3 *for* 1<2 *drinks,* 1.4 *for* 2–3 *and* 2.2 *for over* 3 *drinks per day. The positive association between alcohol and breast cancer was consistent across strata of age, socio-demographic variables, smoking, menstrual, reproductive, and hormonal factors, family history of breast cancer, nutrition and diet indicators. In particular, this study indicated that the alcohol–breast cancer relationship is probably not materially different in younger and older women, that alcohol drinking at an early age is not a particularly clear indicator of subsequent risk, nor that the effect of alcohol is enhanced in thin women. Thus, the findings of this study are both internally consistent and in agreement with most previous evidence, since the relative risks of* 1.3–1.4 *for a consumption of* 10–30 *g of alcohol per day compare well with the corresponding highest intake levels in most American studies. This study is of particular interest, since it provides data on higher levels of alcohol consumption, on which very little information is available. There are nontheless at least three elements which leave open the question of causality: the absence of duration–risk relationship, the inconsistency with evidence from descriptive epidemiology, and the lack of plausible biological mechanisms.*

INTRODUCTION

OVER THE LAST DECADE, a substantial amount of epidemiological evidence has accumulated on alcohol consumption in relation to the risk of breast cancer. The majority of the published studies found a direct relation between alcohol and breast cancer, but there were also some notable exceptions [1, 2].

However, most studies reporting either a positive or no association, and specifically those emanating from the United States, were related to small quantities of alcohol. For instance, the follow-up study of the First National Health and Nutrition Survey [3] found a multivariate relative risk of 2 for consumption of over 5 g of alcohol per day and the American Nurses Health study [4] a relative risk of 1.6 for over 15 g per day. In the study from the American Health Foundation dataset, where no association was observed between alcohol and breast cancer risk [5], the highest level of consumption was 15 g or more per day (i.e. one drink per day or more).

Besides the limitations inherent in many previous studies dealing with low levels of consumption, several other aspects of the possible influence of alcohol on breast carcinogenesis require elucidation. It is important to investigate further the roles of different forms of alcoholic beverage, in different periods of life and in relation to other covariates, particularly body weight or menopausal status, since some studies suggested that the impact of alcohol could be greater for beer and spirits than for wine consumption [6, 7] and greater in (or restricted to) younger, pre-menopausal [3, 4, 6, 7] or leaner women [3, 4].

To provide further documentation on the possible association between alcohol and breast cancer and analyse the potential modifying effect or interaction with other risk factors, this paper presents the updated results from a case-control study conducted

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in Northern Italy, which now includes data on over 2400 cases and 2200 controls from a female population with particularly elevated alcohol consumption *vis-à-vis* other studies.

SUBJECTS AND METHODS

The data were derived from an ongoing case-control study of breast cancer conducted in the greater Milan area, Northern Italy, since January 1983. The general design of this investigation has already been described [8]. Briefly, trained interviewers identified and questioned patients admitted for breast cancer and for a wide spectrum of other conditions to a network of teaching and general hospitals in the greater Milan area. Participation was almost complete, since less than 3% of cases and controls refused to be interviewed. The present report is based on data collected before December 1988.

Cases were women with histologically confirmed breast cancer, diagnosed within the year prior to interview, admitted to the National Cancer Institute and Ospedale Maggiore of Milan, which includes the four largest teaching and general hospitals in the greater Milan area. A total of 2402 cases, aged 23–74 (median age = 53 years) was interviewed.

The *control* group comprised 2220 women, aged 21–74 (median age 54 years), admitted for acute conditions to the same network of hospitals where cases had been identified. Of these, 32% were admitted for traumas, 29% for non-traumatic orthopaedic conditions (chiefly low back pain and disc disorders), 16% had acute surgical conditions and 23% other miscellaneous illnesses, such as skin, eye, nose and throat or dental disorders. The age distribution of cases and controls is given in Table 1.

The structured questionnaire included information on socio-demographic characteristics, general lifestyle habits (e.g. smoking, coffee consumption), a few selected indicator foods, including the major sources of fats, proteins and vitamin A, a problem-oriented medical history and history of use of selected drugs, including oral contraceptives, non-contraceptive oestrogens for treatment of menopausal symptoms, and female hormones for other indications. Questions on alcohol included the number of days per week each type of alcoholic beverage (wine, beer and spirits) was consumed, the average numbers of drinks per day, and the duration of the habit in years.

Table 1. Distribution of 2402 cases of breast cancer and 2220 controls according to age. Milan, Italy, 1983–1988

	Breast Cancer		Controls	
Age group (years)	Number	%	Number	%
<35	98	4.1	156	7.0
35–44	498	20.7	389	17.5
45–54	706	29.4	612	27.6
55–64	633	26.4	614	27.7
65–74	467	19.4	449	20.2

Data analysis and control of confounding

The average number of drinks per day for each type of alcoholic beverage (wine, which by itself accounted for more than 90% of all alcohol consumption in this population, beer and spirits), and the total average alcoholic beverage consumption, assuming a comparable pure alcohol content in each type of drink (i.e. 150 ml of wine = 330 ml of beer = 30 ml of spirits = approximately 10–12 ml of pure alcohol), were computed.

Relative risks (RR) of breast cancer, together with their 95% confidence intervals (CI), were then derived from data stratified for age in decades by the Mantel–Haenszel procedure [9], and significance of linear trend in risk was assessed by means of Mantel's extension test [10]. To simultaneously allow for a number of potential confounding factors, unconditional multiple logistic regression was used, fitted by the method of maximum likelihood [11, 12]. Included in the regression equations were terms

*Table 2. Distribution of 2402 cases of breast cancer and 2220 controls according to various measures of alcohol consumption. Milan, Italy, 1983–1988**

	Breast cancer		Controls	
Variable	Number	%	Number	%
Wine, drinks per day				
0	707	29.4	838	37.8
<1	682	28.4	623	28.1
1<2	751	31.3	620	27.9
2–3	145	6.0	83	3.7
>3	117	4.9	55	2.5
Beer, drinks per day				
0	2182	90.8	2078	93.6
<0.5	160	6.7	103	4.6
0.5–1	40	1.7	27	1.2
>1	20	0.8	12	0.5
Spirits, drinks per day				
0	2181	90.8	2092	94.2
<0.5	148	6.2	95	4.3
0.5–1	62	2.6	31	1.4
>1	11	0.5	2	0.1
Total, alcoholic beverages				
0	665	27.7	804	36.2
<1	640	26.6	610	27.5
1<2	681	28.4	570	25.7
2–3	243	10.1	152	6.8
>3	173	7.2	84	3.8

*For some variable, the sum of strata does not add to the total because of missing values.

for age, geographic area, marital status, education, smoking, age at menarche, menopausal status and age at menopause, nulliparity/age at first birth, oral contraceptive and oestrogen replacement use, and main indicator foods (meat, fats, green vegetables).

RESULTS

Table 2 gives the distribution of women with breast cancer and the comparison group according to reported consumption of various alcoholic beverages. Cases were more frequently wine drinkers (70.6%) than controls (62.2%) and tended to be more frequently heavy drinkers. In this population, consumption of beer and spirits was substantially lower; nonetheless, cases were more frequently drinkers (9.2 vs. 6.4% for beer, 9.2 vs. 5.8% for spirits), and tended to drink more than controls. When total consumption of all alcoholic beverages was considered, 72.3% of cases vs. 63.8% of the controls were drinkers, and 17.3% of cases vs. 10.6% of the controls reported two drinks per day or more.

The relative risk for alcohol drinkers vs. nondrinkers was 1.4 (95% CI = 1.2–1.6). The relative risk in relation to subsequent levels of alcohol consumption are reported in Table 3. With reference to wine consumption, the multivariate relative risk was 1.2 for less than one drink per day, 1.3 for 1<2 drinks, 1.4 for 2–3 drinks, and 2.2 for over 3 drinks per day. For beer, they were 1.5 for both low and moderate consumption, and for spirits 1.4 and 2.0 respectively. The risk estimates for total alcohol consumption were close to those of wine only, being 1.3, 1.3, 1.4 and 2.2 in subsequent levels of intake. When teetotallers were excluded, and the lowest alcohol consumption level was chosen as the reference category, the relative risks for subsequent levels were 1.0, 1.1 and 1.7. All the trends in risk with dose were statistically significant.

Table 4 presents the age-adjusted relative risks for total alcohol consumption in separate strata of age and other selected covariates. No appreciable interaction was observed with age, since the relative risks for the highest consumption category were 1.9, 2.6, 3.6 and 2.4 in subsequent strata of age. The relative risks were similar during the earlier calendar period of data collection (1983–1984, published in a previous paper [8]) and in the subsequent

Table 3. Relative risks of breast cancer in relation to average daily consumption of various types of alcoholic beverages. Milan, Italy, 1983–1988*

	Alcoholic beverage consumption, drinks per day						
	0	<0.5	<1	1<2	2–3	>3	χ^2_1 (trend)
Wine							
M-H*	1‡	—	1.3 (1.1–1.5)	1.4 (1.2–1.7)	2.1 (1.6–2.8)	2.5 (1.8–3.5)	56.41 ($P < 0.001$)
MLR†	1‡	—	1.2 (1.0–1.5)	1.3 (1.1–1.5)	1.4 (1.2–1.6)	2.2 (1.7–2.8)	40.75 ($P < 0.001$)
Beer							
M-H*	1‡	1.4 (1.1–1.8)			1.4 (1.0–2.1)		7.97 ($P = 0.004$)
MLR†	1‡	1.5 (1.1–1.9)			1.5 (1.0–2.3)		9.70 ($P = 0.002$)
Spirits							
M-H*	1‡	1.4 (1.1–1.9)			2.1 (1.4–3.1)		20.33 ($P < 0.001$)
MLR†	1‡	1.4 (1.0–1.9)			2.0 (1.3–3.1)		16.85 ($P < 0.001$)
Total, alcoholic beverages							
M-H*	1‡	—	1.3 (1.1–1.5)	1.3 (1.2–1.7)	1.9 (1.5–2.4)	2.5 (1.9–3.3)	66.16 ($P < 0.001$)
MLR†	1‡	—	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.4 (1.2–1.7)	2.2 (1.7–2.7)	44.21 ($P < 0.001$)
Total, teetotallers excluded							
M-H*	—	—	1‡	1.1 (1.0–1.3)	1.5 (1.2–1.9)	1.9 (1.4–2.5)	26.77 ($P < 0.001$)
MLR†	—	—	1‡	1.0 (0.8–1.2)	1.1 (0.8–1.4)	1.7 (1.3–2.2)	14.39 ($P < 0.001$)

*Mantel–Haenszel estimates adjusted for age in decades.

†Estimates from multiple logistic regression equations including terms for age, geographic area, socio-demographic variables, smoking, menstrual, reproductive and hormonal risk factors for breast cancer, family history, nutrition and diet indicators.

‡Reference category.

Table 4. Relative risks of breast cancer in relation to average daily total alcoholic beverage consumption in separate strata of age and selected covariates. Milan, Italy, 1983–1988*

Variable	Total alcoholic beverage consumption, drinks per day					(Number of cases)†	χ^2_1 (trend)
	0	<1	1<2	2–3	>3		
Age, years							
<45	1‡	1.9	1.5	2.1	1.9	(596)	12.26‖
45–54	1‡	1.2	1.5	1.6	2.6	(706)	19.70‖
55–64	1‡	1.0	1.2	2.8	3.6	(633)	25.85‖
65–74	1‡	1.2	1.6	1.5	2.4	(467)	10.16‖
Calendar period of data collection							
Before June 1984	1‡	1.4	1.2	1.9	2.1	(437)	6.43§
After June 1984	1‡	1.2	1.5	1.7	2.4	(1965)	34.80‖
Smoking habits							
Never smokers	1‡	1.2	1.6	1.8	2.8	(1657)	48.24‖
Ex-smokers	1‡	1.8	1.4	3.4	4.9	(168)	11.47‖
Current smokers	1‡	1.1	1.2	2.0	1.9	(577)	12.16‖
Education (years)							
<7	1‡	1.2	1.5	2.0	2.5	(1265)	41.94‖
7–11	1‡	1.3	1.3	1.8	2.3	(654)	14.33‖
≥12	1‡	1.5	1.5	2.0	2.8	(481)	12.18‖
History of benign breast disease							
No	1‡	1.3	1.4	1.9	2.4	(2085)	40.37‖
Yes	1‡	1.1	1.7	3.4	3.1	(317)	12.29‖
Family history of breast cancer							
No	1‡	1.3	1.4	1.8	2.5	(2131)	55.50‖
Yes	1‡	1.3	1.5	3.3	2.2	(265)	6.65‖
Oral contraceptive use							
Never	1‡	1.3	1.5	2.1	2.6	(2151)	66.29‖
Ever	1‡	1.0	1.3	1.0	2.6	(251)	1.68

*Mantel–Haenszel estimates adjusted for age in decades.
†For some variables, the sum of strata does not add to the total because of missing values.
‡Reference category.
§$P < 0.05$.
‖$P < 0.01$.

dataset. Likewise, the relative risks were comparable in various categories of education (RR = 2.5, 2.3 and 2.8 for the highest level of alcohol consumption), for women without (RR = 2.4) or with (RR = 3.1) a history of benign breast disease, without (RR = 2.5) or with (RR = 2.2) a family history of breast cancer, and never (RR = 2.6) or ever (RR = 2.6) oral contraceptive users. The relative risk was apparently greater among never (RR = 2.8) or ex-smokers (RR = 4.9) than among current smokers (RR = 1.9), but the interaction was not statistically significant.

The modifying effect on alcohol-related risks of main menstrual and reproductive factors are considered in Table 5. The relative risks were comparable across various strata of age at menarche and menopausal status. The point estimates were apparently greater among women with later menopause (RR = 3.8 for the highest level of alcohol consumption), higher parity (RR = 3.6) or later first birth (RR = 3.8), but the heterogeneity across strata, again, was not statistically significant.

Alcohol-related risks in separate strata of body mass index and indicator foods are reported in Table 6. The alcohol-related risks were comparable across strata of body mass index, and not appreciably heterogeneous in relation to different levels of consumption of selected indicator foods (meat, fats, green vegetables), although the alcohol-related risks were apparently higher among more frequent meat consumers.

Table 7 considers selected time-related factors. There was no consistent trend in risk with longer duration of alcoholic beverage consumption, and the risk was not particularly elevated among women who had started to drink alcoholic beverages below age 30.

DISCUSSION

The findings from this hospital-based case-control study of breast cancer confirm that the prevalence of alcohol drinking is elevated among women with breast cancer, that there is a direct dose–risk

Table 5. Relative risks of breast cancer in relation to average daily total alcoholic beverage consumption in separate strata of menstrual and reproductive variables. Milan, Italy, 1983–1988*

Variable	Total alcoholic beverage consumption, drinks per day					(Number of cases)†	χ^2_1 (trend)
	0	<1	1–2	2–3	>3		
Age at menarche							
<15	1‡	1.3	1.4	2.1	2.7	(2055)	48.95§
≥15	1‡	1.1	1.6	1.6	2.4	(342)	10.40§
Menopausal status							
Pre-menopause	1‡	1.6	1.5	2.1	2.3	(1039)	25.40§
Post-menopause	1‡	1.1	1.4	2.8	2.7	(1363)	40.85§
Age at menopause							
<44	1‡	1.1	1.3	2.4	2.0	(258)	7.86§
45–49	1‡	1.1	1.3	1.8	2.8	(383)	12.23§
≥50	1‡	1.1	1.6	1.6	3.8	(722)	22.75§
Number of births							
0	1‡	1.1	1.2	2.0	2.0	(444)	7.68§
1–2	1‡	1.4	1.5	2.0	2.3	(1449)	38.96§
≥3	1‡	1.2	1.5	1.6	3.6	(509)	19.56§
Age at first birth (years)							
<25	1‡	1.1	1.4	1.8	2.2	(790)	21.11§
25–29	1‡	1.8	1.8	2.3	3.2	(751)	30.64§
≥30	1‡	0.9	1.1	1.5	3.8	(417)	7.59§

*Mantel–Haenszel estimates adjusted for age in decades.
†For some variables, the sum of strata does not add to the total because of missing values.
‡Reference category.
§$P < 0.01$.

Table 6. Relative risks of breast cancer in relation to average daily total alcoholic beverage consumption in separate strata of nutritional and dietary indicators. Milan, Italy, 1983–1988*

Variable	Total alcoholic beverage consumption, drinks per day					(Number of cases)†	χ^2_1 (trend)
	0	<1	1<2	2–3	>3		
Body mass index (kg/m^2)							
<20	1‡	1.5	1.6	1.5	2.1	(289)	5.72§
20–24	1‡	1.0	1.3	1.9	2.3	(1198)	27.32§
25–29	1‡	1.6	1.6	2.7	3.1	(680)	32.39§
≥30	1‡	1.6	1.8	1.0	2.1	(227)	3.19
Meat (portions per week)							
<4	1‡	1.1	1.5	1.7	1.9	(729)	16.14§
4–6	1‡	1.4	1.3	1.9	2.3	(794)	16.27§
≥7	1‡	1.4	1.5	2.2	3.4	(879)	33.42§
Fat consumption score							
1 (low)	1‡	1.4	1.4	2.1	2.5	(1181)	33.95§
2 (intermediate)	1‡	1.1	1.5	1.8	2.8	(862)	29.87§
3 (high)	1‡	1.1	1.1	1.6	1.7	(359)	3.17
Green vegetables (portions per week)							
<7	1‡	1.1	1.4	1.6	2.4	(727)	15.48§
7	1‡	1.3	1.4	1.7	2.2	(949)	17.19§
>7	1‡	1.4	1.6	2.6	2.8	(726)	38.40§

*Mantel-Haenszel estimates adjusted for age in decades.
†For some variables, the sum of strata does not add to the total because of missing values.
‡Reference category.
§$P<0.01$

Table 7. Relative risks of breast cancer in relation to duration of alcohol consumption and use of alcohol below age 30. Milan, Italy, 1983–1988*

	Breast cancer	Controls	Relative risk estimates (95% CI)
Duration of alcohol consumption (years)			
Never drinkers	665	804	1†
<20	294	261	1.6 (1.3–2.0)
20–29	485	343	1.7 (1.4–2.0)
30–39	491	364	1.7 (1.4–2.0)
≥40	457	435	1.3 (1.1–1.6)
Unknown	10	13	—
Age at starting drinking			
Never drinkers	665	804	1†
Drinkers, started below age 30	1347	1085	1.4 (1.2–1.7)
Drinkers, started above age 30	375	316	1.4 (1.1–1.7)
Drinkers, age at starting undefined	15	15	—

*Mantel-Haenszel estimates adjusted for age in decades.
†Reference category.

relationship, but there is no evidence of any effect of duration on risk.

The data are of particular interest in consideration of the relatively high alcohol consumption in this Italian population, since there is very little published information on breast cancer risk associated with relatively high levels of intake as are present in the Italian population [3–7]. Further, because of the large number of cases considered, these findings give a more reliable picture than was previously available on potential interactions and modifying effects of other variables.

These findings are in agreement with a previous analysis of the same dataset, based on 437 cases and a similar number of controls, which found a relative risk of 2.1 (with 95% CI = 1.2–3.9) for over 3 drinks per day [8]. The observation of similar risks on subsequent subsets of the study increases the weight of the findings. Further, they are consistent with the majority of other published studies from the United States or Australia, even in quantitative terms of estimated relative risk. The point estimate for 10–15 g of pure alcohol per day, which corresponds to the highest intake levels in most studies conducted in those countries, was in fact 1.3–1.4, which compares well with the estimates from most previous studies [2–7], and rose to 2–2.2 only for over 30 g of ethanol per day which, again, is consistent with the overall evidence from previous studies [7].

A second important elucidation offered by this work is the detailed analysis of subgroups and interactions. Since none of these was significant or consistent, this study indicates that the alcohol–breast cancer relationship is probably not materially different in younger (or pre-menopausal) vs. older women, that alcohol drinking at an early age (below age 30) is not a particularly clear indicator of subsequent risk, nor that the effect of alcohol is enhanced in thin women [3–7]. Thus, the findings of this study are both internally consistent and in agreement with most previous evidence.

Although this is a typical hospital-based case-control study and, as such, has all the related strengths and weaknesses, the frequency of alcohol consumption among the control group was very similar to the population-based data from the 1983 Italian National Health Survey, where non-drinking women in the same age group comprised approximately 40%, and heavy drinkers (>50 g of pure alcohol per day) 2.5% [13, 14]. Further, in this study cases and controls came from comparable catchment areas, participation was almost complete, and allowance for major identified potential confounding factors did not materially modify any of the alcohol-related risks.

If the present data provide further evidence on the association between alcohol and breast cancer in terms of analytical epidemiology, there are at least two elements which leave open the question of causality. First, on an epidemiological level, the absence of association between risk and duration of use, and the inconsistency with evidence from descriptive epidemiology or ecological studies, which found no consistent correlation between measures of alcohol consumption on a population

level and breast cancer rates (although it is rather difficult to separate alcohol drinking by males and females [15, 16]). Second, on a biological level, although several hypotheses have been proposed, there is as yet little evidence of any plausible mechanism(s) by which alcohol consumption might be related to the risk of breast cancer.

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REFERENCES

1. Skegg DCG. Alcohol, coffee, fat, and breast cancer. *Br Med J (Clin Res)* 1987, **295**, 1011–1012.
2. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC. A meta-analysis of alcohol consumption in relation to risk of breast cancer. *JAMA* 1988, **260**, 652–656.
3. Schatzkin A, Jones DY, Hoover RN *et al.* Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first National Health and Nutrition Examination Survey. *N Engl J Med* 1987, **316**, 1169–1173.
4. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987, **316**, 1174–1180.
5. Harris RE, Wynder EL. Breast cancer and alcohol consumption. *JAMA* 1988, **259**, 2867–2871.
6. Harvey EB, Schairer C, Brinton LA, Hoover RN, Fraumeni JF Jr. Alcohol consumption and breast cancer. *J Natl Cancer Inst* 1987, **78**, 657–661.
7. Rohan TE, McMichael AJ. Alcohol consumption and risk of breast cancer. *Int J Cancer* 1988, **41**, 695–699.
8. La Vecchia C, Decarli A, Franceschi S, Pampallona S, Tognoni G. Alcohol consumption and the risk of breast cancer in women. *J Natl Cancer Inst* 1985, **75**, 61–65.
9. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959, **22**, 719–748.
10. Mantel N. Chi square tests with one degree of freedom; extension of the Mantel–Haenszel procedure. *J Am Stat Assoc* 1963, **58**, 690–700.
11. Breslow NE, Day NE. *Statistical Methods in Cancer Research*, Vol. 1, *The Analysis of Case Control Studies*. IARC Sci Publ 1980, **32**, 5–338.
12. Baker RJ, Nelder JA. *The GLIM System. Release 3.* Oxford, Numerical Algorithms Group, 1978.
13. ISTAT (Istituto Centrale di Statistica). Indagine statistica sulle condizione di salute della popolazione e sul ricorso ai servizi sanitari. Novembre 1983. Note e Relazioni, 1986, No. 1.
14. La Vecchia C, Pagano R, Negri E, Decarli A. Determinants of alcohol consumption in Italy. *Int J Epidemiol* 1987, **16**, 295–296.
15. La Vecchia C, Franceschi S, Cuzick J. Alcohol and breast cancer. *Lancet* 1982, **1**, 621.
16. Byers T. Diet and cancer. Any progress in the interim? *Cancer* 1988, **62**, 1713–1724.