NUTRITION AND CANCER, *40*(2), 87–91
Copyright © 2001, Lawrence Erlbaum Associates, Inc.

Dietary Fat Intake and Risk of Epithelial Ovarian Cancer: A Meta-Analysis of 6,689 Subjects From 8 Observational Studies

Michael Huncharek and Bruce Kupelnick

Abstract: *The etiology of epithelial ovarian cancer is unknown. Prior work suggests that high dietary fat intake is associated with an increased risk of this tumor, although this association remains speculative. A meta-analysis was performed to evaluate this suspected relationship. Using previously described methods, a protocol was developed for a meta-analysis examining the association between high vs. low dietary fat intake and the risk of epithelial ovarian cancer. Literature search techniques, study inclusion criteria, and statistical procedures were prospectively defined. Data from observational studies were pooled using a general variance-based meta-analytic method employing confidence intervals (CI) previously described by Greenland. The outcome of interest was a summary relative risk (RR_s) reflecting the risk of ovarian cancer associated with high vs. low dietary fat intake. Sensitivity analyses were performed when necessary to evaluate any observed statistical heterogeneity. The literature search yielded 8 observational studies enrolling 6,689 subjects. Data were stratified into three dietary fat intake categories: total fat, animal fat, and saturated fat. Initial tests for statistical homogeneity demonstrated that hospital-based studies accounted for observed heterogeneity possibly because of selection bias. Accounting for this, an RR_s was calculated for high vs. low total fat intake, yielding a value of 1.24 (95% CI = 1.07–1.43), a statistically significant result. That is, high total fat intake is associated with a 24% increased risk of ovarian cancer development. The RR_s for high saturated fat intake was 1.20 (95% CI = 1.04–1.39), suggesting a 20% increased risk of ovarian cancer among subjects with these dietary habits. High vs. low animal fat diet gave an RR_s of 1.70 (95% CI = 1.43–2.03), consistent with a statistically significant 70% increased ovarian cancer risk. High dietary fat intake appears to represent a significant risk factor for the development of ovarian cancer. The magnitude of this risk associated with total fat and saturated fat is rather modest. Ovarian cancer risk associated with high animal fat intake appears significantly greater than that associated with the other types of fat intake studied, although this requires confirmation via larger analyses. Further work is needed to clarify factors that may modify the effects of dietary fat in vivo.*

Introduction

Ovarian cancer is a major cause of cancer-related morbidity and mortality among women in the United States, with >15,000 deaths occurring annually. This tumor kills more American women than all other gynecological malignancies combined (1). Contributing to the high mortality associated with this tumor is the advanced stage of disease at the time of diagnosis. Early-stage disease is rarely symptomatic, making early detection difficult.

Epithelial carcinomas account for >90% of ovarian neoplasms, with the median age of diagnosis ~63 yr (2). Despite the fact that this tumor represents a disease of great public health importance, little is known regarding its etiology. Prior work suggests that ovarian cancer risk is increased among women with a family history of the disease (3). In addition, parity and oral contraceptive use appear to decrease disease risk (3). The wide variation in incidence worldwide suggests that environmental factors play an important role in the development of ovarian cancer. Diet may represent an environmental determinant of disease risk, although this relationship is uncertain. Some support for this hypothesis comes from international comparisons of food intake that suggest a positive association of ovarian cancer rates with dietary fat intake (4). In addition, migration studies of women emigrating from Japan (a low-risk country) to the Unites States (a high-risk country) show that ovarian cancer rates increase among these women to levels experienced by American women (4).

Although a number of epidemiological studies previously examined the relationship between diet and ovarian cancer risk, the true impact of high fat intake on cancer risk remains obscure. To more clearly define this relationship, a meta-analysis was conducted that pooled all available observational studies examining the relationship between dietary fat

M. Huncharek is affiliated with the Department of Clinical Oncology, Marshfield Clinic Cancer Center, Marshfield, WI 54449; and St. Michael's Hospital Cancer Center, Stevens Point, WI 54481. M. Huncharek and B. Kupelnick are affiliated with the Meta-Analysis Research Group, Stevens Point, WI 54481.

intake and the risk of developing invasive ovarian carcinoma.

Materials and Methods

The methods employed in this analysis have been previously described (5). Briefly, a study protocol was prospectively developed that outlined the purpose and methods of the analysis. Eligibility criteria for studies were determined prospectively, as were the specific data elements to be extracted from each trial. A plan for data analysis was also formulated as part of the study protocol. A data extraction form was designed for recording relevant data from each published study.

Literature retrieval was performed by previously described methods (5). A MEDLARS search was conducted covering January 1966–January 2001. The CancerLit as well as the EMBASE databases were also fully explored, as was the CD-ROM version of Current Contents. The search included all languages. The search terms were risk factors, risk, body weight, diet, and dietary fats linked with ovarian neoplasms. Manual searches of study bibliographies and review of relevant textbooks supplemented electronic database searches. Bibliographies of relevant review articles were also searched. If a series of papers was published, all data were retrieved from the most recent report.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator (oncologist) to exclude those that did not meet protocol-specified inclusion criteria. Reasons for rejection included animal studies, in vitro studies, review articles, letters to the editor, abstracts, non-peer-reviewed articles, and papers dealing with only nonepithelial ovarian tumors. Citations selected from this initial search were subsequently screened for eligibility using the following criteria: 1) observational studies enrolling patients with histologically proven epithelial ovarian tumors excluding tumors of "borderline malignant potential," 2) studies enrolling adult patients only (i.e., ≥18 yr of age), 3) availability of data on dietary fat intake characterized as total fat or stratified by type of fat (e.g., saturated, animal, or unsaturated), and 4) odds ratio or relative risk (RR) with 95% confidence interval (CI) for each study or availability of raw data to calculate these parameters.

Citations meeting the above criteria were entered onto an accept log, and copies of full papers were obtained. Key data elements extracted from each trial included number of cases and controls, type of dietary fat, origin of study subjects (i.e., hospital vs. population based), and factors (if any) used to statistically adjust study odds ratios or RR. Two researchers performed data extraction. Differences in data extraction forms were resolved by consensus.

Statistical Methods

Data analysis was performed according to meta-analysis procedures previously described by Greenland (6). This meta-analysis method is a general variance-based method employing CI. Because the variance estimates are based on adjusted measures of effect and on the 95% CI for the adjusted measure, the CI methods do not ignore confounding and are the preferred methodology for observational data. The estimate of the 95% CI from each study is used to estimate the variance of each study's effect measure, i.e.,

$$\ln \mathrm{RR}_i = \frac{\mathrm{sum}(w_i \times \ln \mathrm{RR}_i)}{\mathrm{sum}\ w_i}$$

where

$$w_i = \frac{1}{\mathrm{variance}\,\mathrm{RR}_i}$$

The RR_i are estimates of RR and, in this instance, have been measured as odds ratios. The variance is estimated from the 95% CI as follows

$$\mathrm{variance}\,\mathrm{RR}_i = \left[\frac{\ln(\mathrm{RR}_i \div \mathrm{RR}_1)}{1.96}\right]^2$$

where RR_i is the estimate of the RR in the *i*th study and RR_1 is the lower bound of the 95% CI for that study.

A 95% confidence limit for the estimated RR is determined as follows

$$95\%\,\mathrm{CI} = e^{\ln\ \mathrm{RR}_s} \pm (1.96 \times \sqrt{\mathrm{variance}_s})$$

and

$$\mathrm{variance}_s = \frac{1}{\mathrm{sum\ weight}_i}$$

Before estimation of a summary RR (RR_s), a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all the studies (4). If Q exceeds the upper tail critical value of χ^2 ($P < 0.05$) at $k - 1$ degrees of freedom (where k is the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e., RR_s) may be of questionable validity. Study effect sizes may be disaggregated by grouping studies into appropriate categories until Q is not rejected within those categories or regression techniques can be employed. That is, reasons for the observed heterogeneity must be sought. In essence, Q is a diagnostic tool for determining whether all the variance in the observed effect sizes is accounted for.

Using the general variance-based meta-analysis method employing CI proposed by Greenland (6), Q is calculated as follows

$$Q = \text{sum}[\text{weight}_i \times (\ln \text{OR}_s - \ln \text{OR}_i)^2]$$

where OR_s and i are estimated as described above.

Results

A total of 123 citations were obtained from the electronic and manual literature searches. Initial screening of these citations yielded 12 that appeared to meet specified protocol inclusion criteria (7–18). Copies of the full manuscripts were obtained for these 12 studies and were reviewed in detail. On further review, four of these did not contain information on dietary fat intake and were, therefore, excluded from the pooled analysis (7–10). The remaining eight studies met protocol inclusion criteria and form the database for the present meta-analysis. Table 1 provides an overview of the included reports.

Overall, 6,689 patients were enrolled in these 8 analyses. All except the study of Kushi et al. (12) were of case-control design. Table 1 lists the odds ratios calculated for each individual report along with its 95% CI. An odds ratio >1 indicates an increased risk of ovarian cancer associated with the highest level of dietary fat intake (compared with the lowest intake level) as defined by the study investigators.

A review of these eight reports revealed that studies differed somewhat on stratification for fat intake. That is, fat intake was characterized as "total fat," "animal fat," "saturated fat," or "monosaturated" or "unsaturated" fat. Because prior studies show little increased risk associated with mono- or unsaturated fats, data were stratified as total, animal, or saturated for pooling in the present meta-analysis (Table 1). As seen in Table 1, most study odds ratios were >1, suggesting a positive association between fat intake and ovarian cancer risk. The exceptions were the results of Kushi et al. (12) for total fat and animal fat and Tzonou et al. (16) for total fat. Despite odds ratios of >1 in most reports, the majority had nonstatistically significant 95% CI (i.e., they included the null value).

As seen in Table 1, seven of the eight studies used total fat as a category for analysis (12–18). Initially, combining the data from these reports yielded an RR_s of 1.26 with a 95% CI of 1.11–1.42. This reflects a 26% greater risk of ovarian cancer among those with the highest vs. the lowest fat intake. An analysis for heterogeneity showed $Q = 17.27$. With six degrees of freedom, a Q of this magnitude is associated with $P = 0.01$. A P value of this size indicates that the data are heterogeneous, making the RR_s of 1.26 of questionable validity.

Sources of heterogeneity were sought by examining the data in Tables 1 and 2. Table 1 provides information regarding factors used to adjust individual study odds ratios, i.e., possible confounders. Because overreporting of consumption by cases may occur, adjustment for total caloric/energy intake would prevent a spurious positive association. Four studies (12,13,16,18) made such adjustments. Pooling these four studies gave $Q = 8.0$. With three degrees of freedom, a Q of this magnitude is associated with $P = 0.04$, a statistically significant result showing persistent heterogeneity. Other factors are accounting for the observed heterogeneity.

Table 2 displays the information used in calculation of Q. The greatest contribution to the value of Q was from the study by LaVecchia et al. (17). This study was a hospital-based analysis with an odds ratio of 2.14 for total fat intake.

Table 1. Overview of Included Studies[a]

Ref.	No. of Cases	No. of Controls	Type of Fat	RR or OR (95% CI)	Adjustments	Hospital or Population-Based
11	215	215	Animal fat	1.83 (1.00–3.38)	Weight/height^2	P
12	139		Total fat	0.80 (0.47–1.36)	Age, total energy intake, no. of live births, age at menopause, family Hx of ovarian cancer, hysterectomy, waist-to-hip ratio, level of physical activity, smoking, education	P
			Animal fat	0.98 (0.57–1.69)		
			Saturated fat	1.17 (0.69–1.97)		
13	450	564	Total fat	1.16 (0.86–1.57)	Age at diagnosis/interview, age, total calorie intake, no. of full-term pregnancies, duration of OC use	P
			Saturated fat	1.20 (1.03–1.40)		
14	172	172	Total fat	2.3 (1.2–4.4)	Education, income, no. of live births, Hx of ovarian cysts, smoking Hx, OC use, IUD use, tubal ligation	P
			Animal fat	1.7 (1.0–3.2)		
15	85	492	Total fat	1.3 (0.7–2.3)	Age, BMI, no. of pregnancies	P
			Saturated fat	1.3 (0.6–2.6)		
16	189	200	Total fat	0.97 (0.73–2.3)	Age, years of schooling, parity, age at 1st birth, menopausal status, energy intake	H
17	455	1,385	Total fat	2.14 (1.39–2.88)	Age, interviewer, marital status, social class, education, parity, age at 1st birth, age at menarche, menopausal status, BMI, OC or other female hormone use	H
18	824	1,132	Total fat	1.86 (1.03–3.37)	Age, education, BMI, smoking, parity, OC use, total energy intake	P

a: Abbreviations are as follows: RR, relative risk; OR, odds ratio; CI, confidence interval; P, population-based; H, hospital; Hx, history; OC, oral contraceptive; IUD, intrauterine device; BMI, body mass index.

Table 2. Data Used in Statistical Analysis for Homogeneity

Ref.	ln OR	Variance	Weight (1/Variance)
11	0.60	0.01	100.00
12	–0.22	0.07	14.29
13	0.15	0.02	50.00
14	0.83	0.11	9.09
15	0.26	0.01	100.00
16	–0.03	0.02	50.00
17	0.76	0.05	20.00
18	0.62	0.09	11.11

Hospital-based studies may produce erroneous results because of numerous biases such as selection bias or differential surveillance. Because this fact may contribute to the observed heterogeneity, a sensitivity analysis was performed by dropping the results of LaVecchia et al. from the meta-analysis and recalculating Q. Q was found to be 11.67. With five degrees of freedom, this gave $P = 0.04$, a marginally statistically significant result showing persistent statistical heterogeneity. Further review of Table 2 indicated that the other hospital-based study by Tzonou et al. (16) contributed ~20% of the observed heterogeneity when all seven studies were pooled. In fact, the results of Tzonou et al., along with those of LaVecchia et al., accounted for >50% of the calculated statistical heterogeneity. A sensitivity analysis was performed dropping both hospital-based studies from the meta-analysis. Q was recalculated and found to be 8.26. For Q of this magnitude, $P = 0.15$, i.e., a nonstatistically significant result. This indicates that the remaining data are homogeneous. Pooling the remaining five studies yielded an RR_s of 1.24 (95% CI = 1.07–1.43), a statistically significant result.

Nonetheless, an additional factor to consider was study type, i.e., case-control vs. cohort. Kushi et al. (12) was the only cohort study, with the remainder being case-control analyses. To examine whether this difference in study type impacted the RR_s, a sensitivity analysis was performed by dropping the results of Kushi et al. and recalculating RR_s. This gave an RR_s of 1.29 (95% CI = 1.01–1.48), a negligible difference compared with the previously calculated RR_s. This demonstrated that cohort vs. case-control design had little influence on the outcome of the meta-analysis. Overall, the data suggest that high fat intake (characterized as total dietary fat, not otherwise specified) is associated with a 24% increased risk of epithelial ovarian cancer vs. low fat intake.

Only three studies stratified subjects by saturated fat intake (12,13,15). These reports had individual odds ratios of 1.17–1.30. Only Risch et al. (13) showed a statistically significant odds ratio. The study of Risch et al. was also the largest of the three, enrolling >1,000 patients (Table 1). Q was calculated before the data from these reports were pooled and found to be 0.79, a nonstatistically significant result. The data could therefore be pooled, since no heterogeneity was found. Collectively, these three reports contained a total of 1,730 subjects. The RR_s for high saturated fat intake was 1.20 (95% CI = 1.04–1.39), a statistically significant result. High saturated fat intake, therefore, is associated with a 20% greater incidence of ovarian cancer than low dietary intake.

The final category of fat intake was animal fat. Three studies provided data on dietary animal fat with a total of 913 subjects (11,12,14). All three reports had nonstatistically significant odds ratios. Combining these data gave an RR_s of 1.70 (95% CI = 1.43–2.03) with $Q = 4.53$ ($P = 0.11$). Although this is a statistically significant result, the overall sample size is relatively small. Because the power of the test for homogeneity is low, the RR_s associated with animal fat intake may require confirmation in larger studies.

Discussion

Despite the fact that epithelial ovarian cancer represents a major cause of cancer-related mortality among women in the United States, its etiology remains poorly understood. Previous epidemiological studies suggest that multiple factors may influence disease risk. These include hormones, environmental exposures, diet, and genetics. Hormonal/reproductive factors such as pregnancy decrease ovarian cancer risk, with multiple births having an increasingly protective effect (15). Conversely, infertility appears to increase disease risk. Use of drugs such as clomiphene to stimulate ovulation is associated with a two- to threefold increase in risk (16).

Although a family history of ovarian cancer is recognized as a risk factor, the vast majority of cases are sporadic. Only ~5% of cases are considered hereditary, in which predisposition for the disease follows a pattern of autonomic dominant transmission with a high degree of penetrance (i.e., a lifetime risk approaching 50%) (17). The evidence supporting a strong environmental role in ovarian cancer development stems largely from the wide international variation in incidence. As alluded to earlier, international comparisons show that incidence rates are positively associated with per capita dietary fat consumption (4), with supporting evidence from several case-control studies.

A limitation of many individual studies is their relatively small sample size, which limits the study's statistical power to detect an effect. Pooling data from multiple observational analyses substantially increases statistical power and may uncover an association not previously demonstrated. In addition, meta-analysis provides a systematic method for evaluating heterogeneity in study outcomes. This provides a basis for determining whether limitations in study design, bias, or uncontrolled confounding contribute to inconsistent or spurious associations. A strength of the meta-analytic methods employed in the present analysis (i.e., general variance-based method employing confidence intervals) is that the effects of confounding are taken into consideration by using adjusted odds ratios in the calculation of a summary estimate of effect. As in the present report, a critical exami-

nation of the individual study-adjusted odds ratios provides important information for sensitivity analyses to explore the influence of factors that may impact study outcome, e.g., lack of adjustment for total caloric intake.

Multiple biases can affect case-control studies. These include referral bias (e.g., when dealing with hospital vs. population-based studies), recall bias, and selection bias, among others. Such biases are not peculiar to case-control analyses and can also occur in cohort studies. Meta-analyses of observational studies require particular attention to observed statistical heterogeneity across studies. In this context, as well as in analyses of randomized trial data, the primary purpose of the meta-analysis is not the determination of a summary estimate of effect but, rather, a thorough evaluation of the reasons underlying the observed heterogeneity. Pooling data in the face of statistical heterogeneity is inappropriate. The heterogeneity must be explained, since any summary estimate of effect in such a situation will be of questionable validity. Our present analysis involved multiple sensitivity tests to investigate heterogeneity across all included reports. The finding that the two hospital-based case-control studies accounted for the statistical heterogeneity suggests that one or more of the above noted biases (or others) (16,17) may be responsible for the variation in outcome of these two reports.

In addition to statistical evidence of association, an association between a suspected etiological agent and a disease end point must be biologically plausible. Risch et al. (13) suggest that "Given the apparent role of pituitary and/or sex hormones in the etiology of ovarian cancer, dietary influences should not be surprising. It seems possible, for example, that circulating estrogen (or progesterone) levels could rise because of biosynthesis from increased dietary cholesterol precursors or from estrogen present in animal meats." They also suggest that dietary fat may also affect prolactin secretions. The hypothesis required confirmation in further studies, although they provide a theoretical framework for the design of laboratory and observational analyses.

The present meta-analysis shows that high dietary fat intake is associated with an ~20–24% increase in ovarian cancer risk. Few studies stratified fat intake as animal fat or saturated fat, and the total number of patients included in the analysis of animal fat was relatively small. Nonetheless, both were positively associated with increased disease risk. Although dietary fat may contribute to the development of this disease, it is likely that the cause is multifactoral. Further work is needed to clearly define the interrelationship between hormonal, reproductive, dietary, and other environmental factors in ovarian carcinogenesis.

Acknowledgments and Notes

Partial funding for this project was provided by a grant from the Marshfield Medical Research Foundation (Marshfield, WI). Address correspondence to M. Huncharek, Meta-Analysis Research Group, 2740 Sunset Blvd., Stevens Point, WI 54481. E-mail: metaresearch@hotmail.com.

Submitted 13 February 2001; accepted in final form 21 May 2001.

References

1. Landis S, Murray T, Bolden S, and Wingo PA: Cancer statistics, 1998. *CA Cancer J Clin* **48,** 6–29, 1998.
2. Parazzini F, Francheschi S, LaVecchia C, and Fasoli M: The epidemiology of ovarian cancer. *Gynecol Oncol* **43,** 9–23, 1991.
3. Whittemore AS, Harris R, and Intyre J: Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* **136,** 1184–1203, 1992.
4. Armstrong B and Doll R: Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. *Int J Cancer* **15,** 617–631, 1975.
5. Cooper H and Hedges LV: *The Handbook of Research Synthesis*. New York: Russell Sage Foundation, 1994.
6. Greenland S: Quantitative methods in review of epidemiologic literature. *Epidemiol Rev* **9,** 1–30, 1986.
7. Mori M and Miyake H: Dietary and other risk factors for ovarian cancer among elderly women. *Jpn J Cancer Res* **79,** 997–1004, 1988.
8. Tomao S, Taggi F, Sberna RCS, and Villani C: Ovarian cancer and dietary habits. *Eur J Gynecol Oncol* **13,** 91–95, 1992.
9. Engle A, Muscat JE, and Harris RE: Nutritional risk factors and ovarian cancer. *Nutr Cancer* **15,** 239–247, 1991.
10. Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, et al.: Reproductive, genetic and dietary risk factors for ovarian cancer. *Am J Epidemiol* **128,** 771–777, 1988.
11. Cramer DW, Welch WR, Hutchinson GB, Willett W, and Scully RE: Dietary animal fat in relation to ovarian cancer risk. *Obstet Gynecol* **63,** 833–838, 1984.
12. Kushi LH, Mink PJ, Folsom AR, Anderson KE, Sheng W, et al.: Prospective study of diet and ovarian cancer. *Am J Epidemiol* **149,** 21–31, 1999.
13. Risch HA, Jain M, Marrett LD, and Howe GR: Dietary fat intake and risk of epithelial ovarian cancer. *JNCI* **86,** 1409–1415, 1994.
14. Shu XO, Gao YT, Yuan JM, Siegler RG, and Brinton LA: Dietary factors and epithelial ovarian cancer. *Br J Cancer* **59,** 92–96, 1989.
15. Slattery ML, Schuman KL, West DW, French TK, and Robinson LM: Nutrient intake and ovarian cancer. *Am J Epidemiol* **130,** 497–502, 1989.
16. Tzonou A, Hsieh C, Polychronopoulou A, Kaprinis G, Toupadaki N, et al.: Diet and ovarian cancer: a case-control study in Greece. *Int J Cancer* **55,** 411–414, 1993.
17. LaVecchia C, Decarli A, Negri E, Parazzini F, Gentile A, et al.: Dietary factors and the risk of epithelial ovarian cancer. *JNCI* **79,** 663–669, 1987.
18. Webb PM, Bain CJ, Purdie DM, Harvey PWJ, and Green A: Milk consumption, galactose metabolism and ovarian cancer (Australia). *Cancer Causes Control* **9,** 637–644, 1998.

Copyright of Nutrition & Cancer is the property of Lawrence Erlbaum Associates and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.