Null Results in Brief

No Association of Consumption of Animal Foods with Risk of Ovarian Cancer

Mandy Schulz,[1] Ute Nöthlings,[1] Naomi Allen,[2] N. Charlotte Onland-Moret,[3] Claudia Agnoli,[4] Dagrun Engeset,[5] Rocco Galasso,[6] Elisabet Wirfält,[7] Anne Tjønneland,[8] Anja Olsen,[8] Kim Overvad,[9] Marie-Christine Boutron-Ruault,[10] Veronique Chajes,[10] Francoise Clavel-Chapelon,[10] Jennifer Ray,[1] Kurt Hoffmann,[1] Jenny Chang-Claude,[11] Rudolf Kaaks,[11] Dimitrios Trichopoulos,[12] Christina Georgila,[13] Pantelina Zourna,[13] Domenico Palli,[14] Franco Berrino,[4] Rosario Tumino,[15] Paolo Vineis,[16] Salvatore Panico,[17] H. Bas Bueno-de-Mesquita,[18] Marga C. Ocké,[18] Petra H.M. Peeters,[3] Eiliv Lund,[5] Inger T. Gram,[5] Guri Skeie,[5] Göran Berglund,[7] Eva Lundin,[19] Göran Hallmans,[20] Carlos A. González,[21] José Ramón Quirós,[22] Miren Dorronsoro,[23] Carmen Martínez,[24] Marie-Jose Tormo,[25] Aurelio Barricarte,[26] Sheila Bingham,[27,28] Kay-Tee Khaw,[27] Timothy J.A. Key,[2] Mazda Jenab,[29] Sabina Rinaldi,[29] Nadia Slimani,[29] and Elio Riboli[29,30]

[1]Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; [2]Cancer Research UK Epidemiology Unit, University of Oxford, Oxford, United Kingdom; [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [4]Nutritional Epidemiology Unit, National Cancer Institute, Milan, Italy; [5]Department of Preventive Medicine, Institute of Community Medicine, University of Tromsø, Tromsø, Norway; [6]Ospedale Oncologico Regionale, Rionero in Vulture (PZ), Italy; [7]Nutritional Epidemiology, Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden; [8]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; [9]University of Aarhus, Institute of Epidemiology and Social Medicine, Aarhus, Denmark; [10]Institut National de la Santé et de la Recherche Médicale, ERI 20, EA4045, and Institute Gustave Roussy, Villejuif, France; [11]German Cancer Research Center, Heidelberg, Germany; [12]Hellenic Health Foundation and [13]Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece; [14]Molecular and Nutritional Epidemiology Unit, Center for Cancer Research and Prevention, Scientific Institute of Tuscany, Florence, Italy; [15]Cancer Registry, Azienda Ospedaliera ''civile M.P. Arezzo'', Ragusa, Italy; [16]Cancer Epidemiology Unit, University of Turin, Turin, Italy; [17]Department of Clinical and Experimental Medicine, Frederico II University, Naples, Italy; [18]National Institute of Public Health and the Environment, Bilthoven, the Netherlands; [19]Department of Medical Biosciences and [20]Department of Public Health and Clinical Medicine, Nutritional Research, Umea University, Umea, Sweden; [21]Department of Epidemiology, Catalan Institute of Oncology, Barcelona, Spain; [22]Public Health and Health Planning Directorate, Asturias, Spain; [23]Direción de salud de Guipúzoa, San Sebastian, Spain; [24]Andalusian School of Public Health, Granada, Spain; [25]Epidemiology Department, Murcia Health Council, Murcia, Spain; [26]Public Health Institute of Navarra, Pamplona, Spain; [27]MRC Dunn Human Nutrition Unit and [28]MRC Centre of Nutritional Epidemiology in Cancer Prevention and Survival, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; [29]IARC, Lyon, France; and [30]Imperial College London, London, United Kingdom

Introduction

A potential role of dietary factors on the risk of ovarian cancer (OVC) has been suggested by ecologic studies due to observed differences in international incidence rates (1). The contribution of dietary factors to the etiology of OVC has been suggested through the modulation of the endogenous hormonal milieu (2, 3) or through antioxidant and anticarcinogenic mechanisms (4). Some case-control studies have suggested that OVC risk is increased with high intakes of fat or dairy products, but the data are inconsistent (5-15). This relates particularly to foods of animal origin and specifically to consumption of fish, dairy products, and meats (16).

Given the paucity of prospective data with a sufficiently large number of cancer cases, we examined animal food consumption as predictors of OVC risk in the large-scale multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) Study.

Materials and Methods

Details of the EPIC Study have been described in detail elsewhere (17). Briefly, study participants from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom), mostly from the general population, were recruited into the study between 1992 and 2000 (366,521 women; 153,521 men). For the present study, females free of any cancer at baseline, with at least one intact ovary, and with non-missing dietary and follow-up information have been included (n = 325,731). All participants signed an informed consent agreement at enrollment. A detailed description of this study population can be found in ref. 18.

At baseline recruitment, habitual diet of the past 12 months was assessed by means of country-specific food frequency questionnaires or diet histories. Foods of animal origin

Cancer Epidemiol Biomarkers Prev 2007;16(4):852–5

Received 1/18/07; revised 1/29/07; accepted 2/12/07.

Grant support: Europe against Cancer Programme of the European Commission; Ligue contre le Cancer, France; Société 3M, France; Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale; German Cancer Aid; German Cancer Research Center; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund of the Spanish Ministry of Health; the participating regional governments and institutions of Spain; Instituto de Salud Carlos III Network Red Centros de Investigación Cooperativa en Epidemiologia y Salud Pública, Spain, grant C03/09; ISCIII, Red de Centros RCESP, C03/09, Spain; Cancer Research United Kingdom; Medical Research Council, United Kingdom; Food Standards Agency, United Kingdom; the Wellcome Trust, United Kingdom; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer; Italian National Research Council; Dutch Ministry of Public Health, Welfare, and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch Zorg Onderzoek Nederland; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; and Norwegian Cancer Society.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Ute Nöthlings, Department of Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbrücke, Arthur-Schneunert-Allee 114-116, 14558 Nuthetal, Germany. Phone: 49-333200-88-724; Fax: 49-33200-88721. E-mail: ute.noethlings@dife.de

doi:10.1158/1055-9965.EPI-07-0054

Table 1. Characteristics of the study population by country

Country	*n*	Number of cases	Person-years	Age at enrollment*
France	65,807	118	553,900.54	51 (43-67)
Italy	29,290	50	181,173.33	50 (35-68)
Spain	23,503	40	155,030.34	47 (34-65)
United Kingdom	50,432	79	275,132.22	47 (21-77)
the Netherlands	26,690	51	176,096.83	52 (21-69)
Greece	14,153	12	52,686.42	52 (29-75)
Germany	27,060	32	158,161.07	48 (35-65)
Sweden	26,298	76	204,773.52	50 (29-72)
Denmark	27,411	86	185,204.59	56 (50-65)
Norway	35,087	37	107,817.80	48 (41-55)
Total	325,731	581	2,049,976.66	50 (24-72)

*Values are median (1st percentile to 99th percentile).

examined in the present study were total meat, fish, eggs and total dairy products and selected subgroups of meat (red meat, poultry, processed meat) and dairy products (milk, yogurt, cheese).

In EPIC, case ascertainment was based upon linkage to cancer registries or active follow-up. To classify ovarian tumors, International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (code C56)

Table 2. Multivariable adjusted hazard ratios (HR) and 95% CI for the association between consumption of animal foods and risk of OVC

Food group*	Categorical analysis						Linear analysis †
	Quintiles of animal food consumption					P_{trend} ‡	
	Q1	Q2	Q3	Q4	Q5		
Total meats (g/day)	<64	64 to <82	82 to <95	95 to <109	≥109		
No. cases/person-years	96/344,627	124/399,470	121/412,212	133/432,282	107/461,386		
HR	1.00 (reference)	0.83	0.82	0.96	0.78	0.68	1.01
95% CI		0.59-1.17	0.57-1.18	0.66-1.40	0.52-1.17		0.87-1.16
Red meat (g/day)	<25	25 to <35	35 to <44	44 to <55	≥55		
No. cases/person-years	95/366,482	116/338,682	122/387,447	134/466,536	114/490,830		
HR	1.00 (reference)	1.22	1.13	1.13	1.04	0.89	0.96
95% CI		0.87-1.69	0.79-1.61	0.78-1.63	0.70-1.56		0.83-1.10
Poultry (g/day)	<8	8 to <13	13 to <18	18 to <23	≥23		
No. cases/person-years	113/404,180	123/387,811	116/382,076	116/438,030	113/437,880		
HR	1.00 (reference)	1.06	1.19	0.99	1.05	0.82	1.04
95% CI		0.80-1.41	0.87-1.61	0.72-1.37	0.75-1.47		0.88-1.21
Processed meat (g/day)	<17	17 to <26	26 to <33	33 to <42	≥42		
No. cases/person-years	92/349,404	127/446,062	129/465,219	119/426,045	114/363,611		
HR	1.00 (reference)	0.98	1.10	1.09	1.25	0.23	1.05
95% CI		0.69-1.37	0.76-1.59	0.74-1.62	0.81-1.92		0.91-1.21
Fish (g/day)	<17	17 to <28	28 to <33	33 to <44	≥44		
No. cases/person-years	94/399,026	119/415,526	125/418,952	127/428,728	116/387,745		
HR	1.00 (reference)	1.10	0.86	0.93	0.90	0.51	1.01
95% CI		0.78-1.53	0.58-1.26	0.62-1.40	0.56-1.43		0.85-1.20
Eggs (g/day)	<9	9 to <11	11 to <13	13 to <16	≥16		
No. cases/person-years	93/363,640	116/393,656	116/435,288	125/435,061	131/422,332		
HR	1.00 (reference)	1.18	1.11	1.29	1.19	0.31	0.97
95% CI		0.87-1.60	0.81-1.52	0.93-1.79	0.85-1.67		0.87-1.08
Total dairy products (g/day)	<131	131 to <156	156 to <185	185 to <209	≥209		
No. cases/person-years	129/368,514	164/392,486	106/382,452	92/444,318	90/462,208		
HR	1.00 (reference)	1.37	1.05	0.63	0.58	0.28	0.89
95% CI		0.93-2.01	0.62-1.77	0.30-1.31	0.26-1.29		0.63-1.24
Milk (g/day)	<55	55 to <114	114 to <173	173 to <264	≥264		
No. cases/person-years	128/444,532	93/383,138	100/408,507	122/417,860	138/396,940		
HR	1.00 (reference)	0.75	0.77	0.84	0.93	0.88	1.03
95% CI		0.56-1.00	0.58-1.01	0.64-1.11	0.70-1.25		0.93-1.14
Yogurt (g/day)	<6	6 to <30	30 to <55	55 to <83	≥83		
No. cases/person-years	125/379,512	90/356,003	101/382,765	122/446,537	143/485,159		
HR	1.00 (reference)	0.75	0.84	0.91	0.90	0.75	1.06
95% CI		0.55-1.01	0.64-1.11	0.69-1.20	0.69-1.19		0.96-1.17
Cheese (g/day)	<19	19 to <28	28 to <36	36 to <44	≥44		
No. cases/person-years	129/388,033	128/418,952	114/402,912	101/406,166	109/433,914		
HR	1.00 (reference)	0.96	1.03	1.00	1.18	0.36	1.04
95% CI		0.69-1.35	0.70-1.51	0.67-1.49	0.77-1.80		0.91-1.18

NOTE: Hazard ratios were adjusted for body mass index, parity, menopausal status, ever use of oral contraceptives, total energy intake, education, smoking, unilateral ovariectomy, and hormone replacement therapy use at baseline.
*Food intakes are calibrated.
† Per increment of 1 SD (total meats: 30.3 g/day; processed meat: 15.6 g/day; poultry: 9.3 g/day; red meat: 18.2 g/day; fish: 17.5 g/day; eggs: 6.6 g/day; total dairy products: 39.4 g/day; milk: 125.7 g/day; yogurt: 44.6 g/day; cheese: 15.6 g/day); additional adjustment for nonconsumer status.
‡ Quintile numbers as continuous variable in regression model.

and International Classification of Diseases O-2 were used. As of April 2004, 620 OVC cases have been reported to the common database at IARC, Lyon. Of those, 581 were primary malignant cancers used for the analysis. Histologic subtype was specified for 61%.

To make dietary exposures comparable across participating countries, dietary intakes were calibrated using a fixed-effects linear model in which center and gender-specific 24-h recall data from an 8% random sample of the total cohort (19) were regressed on questionnaire intakes controlling for covariates (20). Cox's Proportional Hazards models were used to evaluate the association between animal food consumption and OVC occurrence. The models were stratified by study center to control for (unmeasured) center effects. Age was used as the primary time variable with the subjects' age at recruitment as entry time and the subjects' age at diagnosis or censoring (death, emigration, or last complete follow-up) as exit time. Models were controlled for body mass index; total energy intake (continuous); parity (parous, nulliparous); ever use of oral contraceptives; hormone replacement therapy (yes, no, unknown); menopausal status (pre-, postmenopausal, not defined); education (three categories); smoking (never, ever, unknown); and unilateral ovariectomy (yes, no). All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. We calculated a power of 95% to detect a significant hazard ratio (HR) of $\geq$1.5 for the highest versus the lowest quintile (α = 0.05; ref. 21).

Results

Baseline characteristics of the study population can be found in Table 1. We observed no significant association between the major animal food groups (total meat, eggs, fish, total dairy products) and risk of OVC, neither with the quintile analysis nor with the linear analysis (Table 2). In addition, meat subgroups (red meat, poultry, processed meat) and dairy products (milk, yogurt, cheese) did not show any relationships with incident OVC (Table 2). Further adjustment for fruit and vegetables or other animal products made little difference to these estimates (data not shown). We found no evidence for effect modification by menopausal status, ever oral contraceptives use, and baseline hormone replacement therapy use for any of the animal foods. Nulliparous women seemed to benefit from a high consumption of total dairy products [HR, 0.37; 95% confidence interval (95% CI), 0.14-0.97, per increment of 39.4 g/day (1 SD)] compared with parous women (HR, 1.01; 95% CI 0.69-1.47; $P_{\text{interaction}}$ = 0.0025); however, none of the dairy subgroups nor other animal foods showed significant associations. Histology-specific [serous (n = 228), mucinous (n = 51), endometrioid tumors (n = 56)] models yielded mostly nonsignificant risk estimates except for associations between serous tumors, total meat and poultry (HR, 1.27; 95% CI, 1.02-1.60; and HR, 1.31; 95% CI, 1.07-1.61 per increment of 1 SD in intake, respectively; data not shown).

Exclusion of women who were diagnosed within 1 year of recruitment (n = 81) did not materially change these associations.

Discussion

The present study on >325,000 European women does not provide evidence for an association between consumption of animal foods (meat, fish, eggs, dairy products) and risk of OVC. Although cohort evidence is still limited, a direct association between meat consumption and OVC risk has been suggested in several case-control studies (10, 12, 15, 22-24). Egg consumption has been related to OVC in most of the cohort studies (25-27) but not all (28). To date, there is only one prospective analysis of fish consumption and OVC risk reporting a null finding (28), whereas an inverse association was indicated by several case-control studies (8, 22, 29). With respect to dairy foods, study results are mixed (9, 12, 14, 15, 22, 23, 26, 30-33).

To our knowledge, this is the largest prospective study to report on a variety of animal foods in relation to OVC risk. Apart from its large sample size, its specific strength is the wide variation in food consumption due to the multicenter design of EPIC. Limitations of the study include the potential of misreported food consumption, which could have obscured weak associations.

In conclusion, in the present study, we found no evidence of a significant association between animal food consumption and OVC risk. Our findings from subgroup analyses (parous versus nulliparous women; histology-specific analysis) need confirmation in future studies because the number of cases per subgroup was relatively small, and we cannot rule out that these findings might have occurred by chance.

References

1. Parkin DM. Cancers of the breast, endometrium and ovary: geographic correlations. Eur J Cancer Clin Oncol 1989;25:1917–25.
2. Thomas HV, Davey GK, Key TJ. Oestradiol and sex hormone-binding globulin in premenopausal and post-menopausal meat-eaters, vegetarians and vegans. Br J Cancer 1999;80:1470–5.
3. Bennett FC, Ingram DM. Diet and female sex hormone concentrations: an intervention study for the type of fat consumed. Am J Clin Nutr 1990;52:808–12.
4. Lampe JW. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am J Clin Nutr 1999;70:475–90S.
5. Bidoli E, La Vecchi C, Montella M, et al. Nutrient intake and ovarian cancer: an Italian case-control study. Cancer Causes Control 2002;13:255–61.
6. Bosetti C, Negri E, Franceschi S, et al. Olive oil, seed oils and other added fats in relation to ovarian cancer (Italy). Cancer Causes Control 2002;13:465–70.
7. Byers T, Marshall J, Graham S, Mettlin C, Swanson M. A case-control study of dietary and nondietary factors in ovarian cancer. J Natl Cancer Inst 1983;71:681–6.
8. Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr 1999;70:85–90.
9. Goodman MT, Wu AH, Tung KH, et al. Association of dairy products, lactose, and calcium with the risk of ovarian cancer. Am J Epidemiol 2002;156:148–57.
10. La Vecchia C, Decarli A, Negri E, et al. Dietary factors and the risk of epithelial ovarian cancer. J Natl Cancer Inst 1987;79:663–9.
11. McCann SE, Moysich KB, Mettlin C. Intakes of selected nutrients and food groups and risk of ovarian cancer. Nutr Cancer 2001;39:19–28.
12. Mori M, Miyake H. Dietary and other risk factors of ovarian cancer among elderly women. Jpn J Cancer Res 1988;79:997–1004.
13. Parazzini F, Chatenoud L, Chiantera V, et al. Population attributable risk for ovarian cancer. Eur J Cancer 2000;36:520–4.
14. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Hernandez-Avila M. Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico. Oncology 2002;63:151–7.
15. Zhang M, Yang ZY, Binns CW, Lee AH. Diet and ovarian cancer risk: a case-control study in China. Br J Cancer 2002;86:712–7.
16. Schulz M, Lahmann PH, Riboli E, Boeing H. Dietary determinants of epithelial ovarian cancer: a review of the epidemiologic literature. Nutr Cancer 2004;50:120–40.
17. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
18. Schulz M, Lahmann PH, Boeing H, et al. Fruit and vegetable consumption and risk of epithelial ovarian cancer: the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2005;14:2531–5.
19. Slimani N, Ferrari P, Ocke M, et al. Standardization of the 24-hour diet recall calibration method used in the European Prospective Investigation into Cancer and Nutrition (EPIC): general concepts and preliminary results. Eur J Clin Nutr 2000;54:900–17.
20. Ferrari P, Kaaks R, Fahey MT, et al. Within- and between-cohort variation in measured macronutrient intakes, taking account of measurement errors, in the European Prospective Investigation into Cancer and Nutrition study. Am J Epidemiol 2004;160:814–22.
21. Breslow NE, Day NE. Statistical methods in cancer research, vol. II. The design and analysis of cohort studies. IARC Scientific Publications No. 82. Lyon: 1987.
22. Bosetti C, Negri E, Franceschi S, et al. Diet and ovarian cancer risk: a case-control study in Italy. Int J Cancer 2001;93:911–5.
23. Mori M, Harabuchi I, Miyake H, et al. Reproductive, genetic, and dietary risk factors for ovarian cancer. Am J Epidemiol 1988;128:771–7.

24. Tavani A, La Vecchia C, Gallus S, et al. Red meat intake and cancer risk: a study in Italy. Int J Cancer 2000;86:425–8.
25. Snowdon DA. Diet and ovarian cancer. JAMA 1985;254:356–7.
26. Kushi LH, Mink PJ, Folsom AR, et al. Prospective study of diet and ovarian cancer. Am J Epidemiol 1999;149:21–31.
27. Bertone ER, Rosner BA, Hunter DJ, et al. Dietary fat intake and ovarian cancer in a cohort of US women. Am J Epidemiol 2002;156:22–31.
28. Larsson SC, Wolk A. No association of meat, fish, and egg consumption with ovarian cancer risk. Cancer Epidemiol Biomarkers Prev 2005;14:1024–5.
29. Cramer DW, Welch WR, Hutchison GB, Willett W, Scully RE. Dietary animal fat in relation to ovarian cancer risk. Obstet Gynecol 1984;63:833–8.
30. Fairfield KM, Hankinson SE, Rosner BA, et al. Risk of ovarian carcinoma and consumption of vitamins A, C, and E and specific carotenoids: a prospective analysis. Cancer 2001;92:2318–26.
31. Engle A, Muscat JE, Harris RE. Nutritional risk factors and ovarian cancer. Nutr Cancer 1991;15:239–47.
32. Webb PM, Bain CJ, Purdie DM, Harvey PW, Green A. Milk consumption, galactose metabolism and ovarian cancer (Australia). Cancer Causes Control 1998;9:637–44.
33. Yen ML, Yen BL, Bai CH, Lin RS. Risk factors for ovarian cancer in Taiwan: a case-control study in a low-incidence population. Gynecol Oncol 2003;89: 318–24.