

Fruit and Vegetable Consumption and Risk of Epithelial Ovarian Cancer: The European Prospective Investigation into Cancer and Nutrition

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Abstract

Objective: The association between consumption of fruit and vegetables and risk of ovarian cancer is still unclear from a prospective point of view.

Methods: Female participants ($n = 325,640$) of the European Prospective Investigation into Cancer and Nutrition study, free of any cancer at baseline, were followed on average for 6.3 years to develop ovarian cancer. During 2,049,346 person-years, 581 verified cases of primary, invasive epithelial ovarian cancer were accrued. Consumption of fruits and vegetables as well as subgroups of vegetables, estimated from validated dietary questionnaires and calibrated thereafter, was related to ovarian cancer incidence in multivariable hazard regression models. Histologic subtype specific analyses were done.

Results: Total intake of fruit and vegetables, separately or combined, as well as subgroups of vegetables (fruiting, root, leafy vegetables, cabbages) was unrelated to risk of ovarian cancer. A high intake of garlic/onion vegetables was associated with a borderline significant reduced risk of this cancer. The examination by histologic subtype indicated some differential effects of fruit and vegetable intake on ovarian cancer risk.

Conclusion: Overall, a high intake of fruits and vegetables did not seem to protect from ovarian cancer. Garlic/onion vegetables may exert a beneficial effect. The study of the histologic subtype of the tumor warrants further investigation. (Cancer Epidemiol Biomarkers Prev 2005; 14(11):2531–5)

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Introduction

Among female cancers, ovarian cancer is less common than cancer of the breast and the uterus (1). Nevertheless, due to its very high case fatality rate (2), ovarian cancer accounts for almost half of the deaths of gynecologic cancer mortality and is the fourth leading cause of death of cancer mortality among women from Northern and Western Europe, Australia, and North America (3). Various reproductive and lifestyle characteristics have been shown to influence risk of ovarian cancer. Among the strongest established epidemiologic factors are parity and oral contraceptive use, which confer a long-lasting protection against the disease. The potential role of dietary factors on risk of ovarian cancer was proposed first by ecological studies that related country-specific aggregate dietary data to cancer incidence and mortality rates (4-7). These studies suggested that a high intake of fat, milk, and eggs may be associated with an increased risk for ovarian cancer, whereas a high intake of fruits and vegetables may be related to a decreased risk. Individual-level epidemiologic studies, however, have not uniformly confirmed these relationships (8). Case-control findings globally suggest an inverse association of vegetable intake with ovarian cancer risk, but the results on fruits are not consistent (9-13). To date, there have been only three prospective studies that reported on fruit and vegetable intake and ovarian cancer risk (14-16), and these showed only a very weak inverse association of risk with intake of vegetables and no association or a slightly positive association with fruit consumption. Thus far, the most consistent association that has emerged from both case-control and cohort studies is the protective effect of green leafy vegetables (9, 14, 17, 18), but the role of other vegetable subgroups on risk of ovarian cancer, such as cruciferous or allium vegetables, remains to be established.

Epithelial ovarian cancer has several histologic subtypes, the major ones being serous, endometrioid, and mucinous subtypes (19). It has been shown that the effect of risk factors on disease risk, such as parity, use of oral contraceptives (20, 21), anthropometric factors (22), and selected dietary factors (23), may vary according to the histologic subtype of the tumors. Currently, no prospective epidemiologic study has addressed the effect of fruit and vegetable consumption according to major histologic subtypes of ovarian malignancies.

The objective of the present analysis was to investigate whether a high consumption of fruit and vegetable is associated with a decreased risk of ovarian cancer using data from a large-scale multicenter cohort study (European Prospective Investigation into Cancer and Nutrition, EPIC). We specifically aimed to examine the relationships between consumption of subgroups of vegetables and risk of ovarian cancer, in total and by histologic subtype.

Materials and Methods

Study Population. The EPIC study is a multicenter prospective cohort study designed to investigate the relationships between diet, lifestyle, and environmental factors and the incidence of different cancers. The methods have been described in detail elsewhere (24). The EPIC cohort consists of subcohorts from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, the United Kingdom), which were recruited between 1992 and 2000 (366,521 women and 153,457 men). The study participants were recruited from the general population except in France (females of the health insurance for state school employees); in Utrecht (women attending breast cancer screening); Ragusa (blood donors and their spouses); and in Oxford ("health conscious" group, mostly vegetarians).

Table 1. Description of the study cohorts participating in the EPIC Study

Center, country	Cohort size (n)	Age at enrollment (y)*	Ovarian cancer cases (n)	Person-years
France	65,738	51 (41-71)	118	553,343
Italy	29,291	50 (29-77)	50	181,177
Spain	23,500	47 (29-69)	40	155,013
United Kingdom	50,418	47 (20-98)	79	275,076
The Netherlands	26,690	52 (20-70)	51	176,086
Greece	14,154	52 (20-84)	12	52,685
Germany	27,060	48 (19-70)	32	158,166
Sweden	26,292	50 (29-73)	76	204,735
Denmark	27,431	56 (50-65)	86	185,312
Norway	35,066	48 (40-55)	37	107,753
Total	325,640	51 (19-98)	581	2,049,346

*Median (min-max).

For the present analysis, female subjects from all EPIC centers were included (Table 1). A priori exclusion criteria were prevalent cancer of any site ($n = 19,953$), bilateral ovariectomy ($n = 10,560$), and missing follow-up ($n = 1,293$). Furthermore, subjects with no dietary assessment ($n = 2,554$), subjects lacking nondietary information, and subjects ranking in the top and bottom percentile of energy intake to energy expenditure ratio ($n = 6,472$) were excluded from the analysis to reduce the effect on the analysis of implausible extreme values. In addition, subjects with a diagnosis after the censoring date were excluded ($n = 49$), leaving 325,640 females for the analysis. End of follow-up time was determined by either a diagnosis of ovarian cancer or censoring (death, emigration, or last complete follow-up).

Dietary and Lifestyle Questionnaires. At the baseline examination, the participants' habitual diet of the past 12 months was assessed by means of country-specific validated food frequency questionnaires with the exception of Malmö, Sweden, where a modified diet history method was used (24). The food frequency questionnaire was self-administered in almost all centers, except in Greece and Ragusa, Spain, where interviewer-administered questionnaires were used. To make dietary exposures comparable across centers, dietary intakes from questionnaires were calibrated. For this purpose, a single 24-hour dietary recall was collected from an 8% random sample of the total cohort, using a standardized computerized recall method developed for EPIC (25).

The fruit and vegetable variables examined in the present analysis were total fruits and vegetables, total fruits, total vegetables, and selected subgroups, which could be investigated separately: fruiting vegetables, root vegetables, leafy vegetables, cabbages, mushrooms, and garlic/onion vegetables. The total fruit consumption category mainly consisted of the intake of all sorts of fresh fruits (~90%) but included dried and canned fruits as well. Not included in total vegetables or total fruits were potatoes and other tubers, legumes, and fruit and vegetable juices, respectively. Details of food items included in the selected vegetable subgroups used in the present analysis have been reported in full by Agudo et al. (26). Lifestyle questionnaires were administered by collecting information on education, medical history (surgeries and previous illnesses), tobacco and alcohol consumption, physical activity, menstrual and reproductive history, use of oral contraceptives, and hormone replacement therapy. Height and weight were measured at the baseline examination, except for the Oxford "health conscious," the Norwegian cohort, and approximately two thirds of the French cohort, from whom self-reports were obtained.

Case Ascertainment. Most countries based their follow-up upon linkage to cancer registries to ascertain new cancer cases.

In France, Germany, and Greece, follow-up was based on a combination of methods, including health insurance, cancer and pathology registries, and active follow-up through study participants and their next-of-kin. Furthermore, mortality data were collected from either the cancer registries or the mortality registries. To classify ovarian tumors, the 10th Revision of the International Statistical Classification of Diseases (code C56) and the second version of the International Statistical Classification of Diseases for Oncology was used. Ovarian tumors were further classified according to histology. By the end of April 2004, 620 ovarian cancer cases had been reported to the common database at the IARC, Lyon, based on complete follow-up with censoring periods ending between December 2001 and December 2002 in most of the centers. After exclusion of *in situ* and metastatic ovarian tumors, 581 cases of epithelial ovarian tumors (primary, malignant, or borderline malignant) remained and were available for this analysis: 228 were serous tumors, 51 mucinous, 56 endometrioid, 22 clear cell, nine transitional cell or undifferentiated, and 137 were not otherwise specified or could not be classified; histology information was missing for 78 cases.

Covariates. In the present analysis, we considered the following covariates assessed at baseline: body mass index (kg/m^2), menopausal status (premenopausal, perimenopausal, postmenopausal, or undefined), unilateral ovariectomy (yes/no), education (no or primary school, more than primary school, not specified), smoking (never, ever, not specified), current alcohol consumption (abstainers, 1-15, 15-30, ≥ 30 g/d), current hormone replacement therapy use (yes, no, not specified), ever pill use (yes, no, not specified), parity (nulliparous, parous, not specified), age at menarche (≤ 11 , 12, 13, 14, ≥ 15 years), energy intake from fat sources (kcal/d), energy intake from nonfat sources (kcal/d), and leisure physical activity.

Statistical Analysis. Vegetable and fruit intakes (g/d) were estimated from the dietary questionnaires. These intakes were linearly calibrated according to the calibration methodology applied in EPIC (27). To summarize briefly, dietary intakes were calibrated using a fixed effects linear model in which gender- and center-specific 24-hour dietary recall data were regressed on the questionnaire data controlling for covariates (weight, height, age, season of administration of dietary questionnaires). A set of weights was used to model the effect of season and the day (weekdays versus weekend days) when the 24-hour recall was obtained. Zero consumption values in the dietary questionnaires were excluded from the regression calibration models and kept as zero values. Negative values occasionally occurring after calibration were set to zero in the calibrated data set. Energy intake was calibrated the same way.

We estimated hazard ratios and 95% confidence intervals using Cox regression to evaluate the association between fruit and vegetable intake and risk of ovarian cancer. The models were stratified by center to control for differences in questionnaire design, follow-up procedures, and other (unmeasured) center effects. Age was used as the primary time variable in the counting process formulation with entry time t_0 defined as the subject's age at recruitment and exit time t_1 defined as the subject's age at ovarian cancer diagnosis or censoring date. On the continuous scale of the fruit and vegetable variables, results were obtained for both uncalibrated and calibrated intakes. We controlled our models for body mass index, energy from fat sources, energy from nonfat sources, nonconsumer status, unilateral ovariectomy, hormone replacement therapy use, education, alcohol intake, menopausal status, parity, and smoking, which were found to affect the association. Furthermore, the latter three covariates were evaluated as potential effect modifiers, and stratified analyses were conducted. However, the stratified

analyses did not reveal marked differences in risk across strata, and tests for interaction failed to reach statistical significance (data not shown). Ever use of oral contraceptives, age at menarche, and leisure physical activity were found to not affect the association.

Cubic spline regression (28) was used to investigate non-linearity of the relative risk function.

All statistical tests were two sided, and $P < 0.05$ was considered statistically significant. Analyses were done with SAS for Windows, version 9.1 (SAS Institute, Cary, NC).

Results

During a mean follow-up time of 6.3 years, >2 million person-years were accrued and 581 incident cases of epithelial ovarian cancer (Table 1). Mean daily intake of fruits and vegetables varied considerably across the EPIC centers and has been presented in full by Agudo et al. (26). Briefly, in this study, the Southern European countries (Greece, France, Italy, Spain) had higher fruit and vegetable intakes (>430 g/d) than the Western European countries (Germany, the Netherlands, the United Kingdom) and Denmark (330-417 g/d) and than Norway and Sweden (<300 g/d). The highest consumption of leafy vegetables and fruiting vegetable was observed in Navarra, Spain (57 g/d) and in Murcia, Spain (146 g/d), respectively. Mean daily intake of root vegetables was highest in the Norwegian centers (41 g/d) and of cabbages in Cambridge, United Kingdom (34 g/d). The Spanish center Murcia was found to have the highest intake of garlic/onion vegetables (43 g/d). Consumption of mushrooms was low across all centers (0-6 g/d).

In multivariate models, the effect of an increase in fruits and vegetables was estimated first for the original (uncalibrated) and second for the calibrated intake (Table 2). Using calibrated data, risk estimates were somewhat stronger, but simultaneously, confidence limits became wider resulting in non-significant estimates, when compared with the original data. Focusing on all ovarian tumors, there was a weak positive association between total fruit intake and cancer risk, which was statistically significant with the uncalibrated data. In addition, results indicate an inverse association with garlic/onion vegetables. Although this association was not statistically significant after calibration, an increment of 8 g/d resulted in a 21% decrease in risk.

The separate analysis by histologic subtype suggested some differences in the association (Table 2). Fruit intake seemed positively related to incidence of mucinous ovarian tumors, whereas an inverse association with risk of endometrioid ovarian cancer was observed. Consumption of vegetables in contrast was found to be inversely related to mucinous ovarian cancer (35% risk reduction with every 80 g increment) but was not associated with serous and endometrioid ovarian cancer risk. The same held true for consumption of fruiting vegetables. The suggested inverse association of garlic/onion vegetables seemed confined to serous tumors. However, none of the risk estimates reached statistical significance, and tests for heterogeneity of risk measures across histologic subtypes failed to reject homogeneity of risk.

For total fruit and vegetable consumption, combined or separately, cubic spline regression models were fit to investigate a potential dose-response relationship (data not shown). Concerning total fruit and vegetable intake, the cubic spline regression indicated an increased risk for ovarian cancer among low consumers: risk markedly declined up to an intake of about 250 g/d and leveled off thereafter showing no benefit of higher intakes. With respect to fruit consumption, there was evidence for an increased risk of ovarian cancer for both low (<150 g/d) and high intake (>250 g/d).

Table 2. Multivariate hazard ratios and 95% confidence intervals based on uncalibrated and calibrated intakes of fruits and vegetables for all ovarian cancers and calibrated intakes by histologic subtype

Food group (per g increment)	Hazard ratio (95% confidence interval)				
	All ovarian tumors		Histologic subtype		
	Uncalibrated	Calibrated	Serous*	Mucinous [†]	Endometrioid [‡]
Total fruits and vegetables (per 80 g)	1.01 (0.98, 1.04)	1.02 (0.95, 1.10)	1.07 (0.95, 1.19)	1.10 (0.88, 1.37)	0.87 (0.68, 1.11)
Total fruits (per 80 g)	1.04 (1.00, 1.08)	1.08 (0.99, 1.18)	1.14 (0.99, 1.31)	1.26 (0.98, 1.62)	0.76 (0.54, 1.08)
Total vegetables (per 80 g)	0.95 (0.90, 1.02)	0.92 (0.76, 1.11)	0.95 (0.70, 1.29)	0.65 (0.32, 1.34)	1.00 (0.56, 1.79)
Fruiting vegetables (per 40 g)	0.97 (0.90, 1.04)	0.97 (0.80, 1.16)	1.11 (0.85, 1.44)	0.60 (0.29, 1.26)	1.07 (0.63, 1.81)
Root vegetables (per 20 g)	1.00 (0.94, 1.05)	1.05 (0.91, 1.22)	1.07 (0.87, 1.33)	0.89 (0.52, 1.54)	1.06 (0.69, 1.63)
Leafy vegetables (per 8 g) [§]	0.99 (0.97, 1.02)	0.98 (0.90, 1.07)	1.01 (0.88, 1.17)	0.87 (0.61, 1.24)	1.11 (0.86, 1.42)
Cabbages (per 8 g)	1.00 (0.98, 1.02)	1.00 (0.90, 1.11)	1.05 (0.91, 1.22)	1.05 (0.78, 1.40)	0.90 (0.63, 1.29)
Mushrooms (per 1 g) [¶]	1.00 (0.99, 1.01)	1.02 (0.97, 1.07)	1.02 (0.95, 1.10)	1.05 (0.96, 1.15)	0.87 (0.70, 1.08)
Garlic/onion (per 8 g) ^{**}	0.93 (0.86, 1.00)	0.79 (0.62, 1.01)	0.73 (0.50, 1.08)	1.36 (0.76, 2.41)	0.87 (0.44, 1.71)

NOTE: Adjusted for age, center, body mass index, energy from fat sources, energy from nonfat sources, unilateral ovariectomy, parity, menopausal status, education, smoking, alcohol drinking, hormone replacement therapy use, and nonconsumer status (0/1).

*Estimates based on calibrated data ($n = 228$ cases).

[†]Estimates based on calibrated data ($n = 51$ cases).

[‡]Estimates based on calibrated data ($n = 56$ cases).

[§]Estimates only for selected centers: Norway excluded.

^{||}Estimates only for selected centers: Umeå excluded.

[¶]Estimates only for selected centers: Umeå and Norway excluded.

**Estimates only for selected centers: France, Umeå, and Norway excluded.

These associations were more pronounced for serous than for nonserous tumors. There was no association between vegetable consumption alone and ovarian cancer risk when cubic spline regression was applied.

Finally, we calculated country-specific risk estimates for those countries contributing at least 50 cases to the total number of cases (France, Italy, the United Kingdom, the Netherlands, Denmark, and Sweden). There was no evidence of heterogeneity across countries when we examined all ovarian cancer cases. In addition, results were unchanged if early diagnosed cases (<1 year after baseline) or borderline malignant tumors, respectively, were excluded from the analysis.

Discussion

Fruits and vegetables comprise a diverse food group characterized mostly by low energy density and specific potentially anticarcinogenic and antioxidant compounds. A protective effect from high consumption of fruits and vegetables has been suggested for several cancers, including ovarian cancer (29). The biological rationale for this effect is strong insofar as the role of antioxidants in blockage or repair of cell damage due to oxidants is well established (30-32). A recent review on dietary determinants of ovarian cancer concluded that a possible benefit may come from vegetable consumption rather than from fruit consumption (8).

The present study based on a cohort of >325,000 European women did not provide evidence for an inverse association between overall fruit and vegetable consumption and risk of ovarian cancer. This is mostly consistent with other prospective study findings (14-16); only one cohort study observed a statistically significant inverse association between vegetable consumption and ovarian cancer risk (16). In contrast, a considerable number of case-control studies reported a significant decrease in risk for high vegetable intake (9-13), whereas others did not (33, 34). Most of the previous studies reported a nonsignificant association with fruit intake. Considering the overall null associations we observed in the present study, the lack of a linear relationship between fruit and vegetable consumption and risk of ovarian cancer may be suggested. Yet, we found some evidence for a dose-response relationship in that low consumers may be at an increased risk

for ovarian cancer. In addition, our data suggest that vegetable subgroups as well as histology of the tumor may play a differential role in ovarian carcinogenesis.

Examining the effect of subgroups of vegetables on cancer risk seems valuable, because specific vegetables contain different bioactive compounds, such as glucosinolates in cruciferous vegetables or sulfur compounds in allium vegetables. This study indicated a risk-reducing association with high intake of garlic/onion vegetables. Although the protective role of garlic/onion vegetables was not an *a priori* hypothesis in the present study and we cannot rule out the possibility of a chance finding, this result deserves some attention. A protective effect of these vegetables has recently been reported by Zhang et al. (13) presenting data from a case-control study in China. However, an earlier case-control study in the same study area did not reveal a protective effect (33). To our knowledge, there is no other prospective study that reported on allium consumption with regard to ovarian cancer risk. There is a strong biological background explaining the beneficial effect of allium on cancer risk, which has especially been shown for cancers of the stomach and the colorectum (35). Organosulfur compounds and mainly allyl derivatives, which are known to inhibit carcinogenesis and prominent substances in allium vegetables, are thought to be related to protection from cancer (36, 37). Although exact mechanisms are not clear, properties, such as modulation of the activity of metabolizing enzymes and antiproliferative activity and therewith inhibition of cell proliferation and tumor growth, exhibit possible mechanisms to protect from ovarian cancer (38, 39). With regard to other vegetable subgroups, findings of this analysis do not confirm a protective effect of consumption of green leafy vegetables on ovarian cancer risk, which has been suggested by Kushi et al. (14), nor did any association with fruiting, root, or cruciferous vegetables become apparent.

Fruit and vegetable consumption may exhibit different effects on cancer risk depending on histologic subtype of the tumor. Because it is known that the mucinous subtype generally has a poorer prognosis than ovarian tumors of another histologic type (40), it is all the more important to identify foods that may protect from this specific type of tumor. In this study, a high intake of total vegetables and fruiting vegetables was associated, to some extent, with a reduced risk of mucinous ovarian cancer. However, these findings need to be confirmed in future studies. The inverse

association of garlic/onion vegetables may be confined to serous tumors. Serous tumors comprise the largest proportion of ovarian cancers, which may have affected the chance to detect an association. There is one cohort study from Sweden (16) that included vegetable subgroups in combination with histologic subtypes (serous versus nonserous). However, risk estimates were reported for all cases only, because they did not differ between serous and nonserous ovarian tumors.

To our knowledge, this is the first prospective study to report on a variety of vegetable subgroups taking histology of the ovarian tumor into account and to suggest different effects on ovarian cancer risk according to these aspects. Specific strengths of our study are its large sample size, which enables us to accrue a relatively high number of cases, and its wide variation in fruit and vegetable consumption due to the multicohort design of EPIC. However, limitations of the study include the potential of misreported fruit and vegetable intake. It is known that foods considered as salubrious, such as fruits and vegetables, are overreported by study subjects (41, 42). Unlike case-control studies, in this prospective study, case status can be ruled out to having influenced the reported intake. However, subjects with an overall poor diet may have overreported their fruit and vegetable consumption to a larger degree than subjects with a healthy diet. This would attenuate the association between fruit and vegetable consumption and ovarian cancer risk. In addition, habitual diet of the past 12 months may not be associated with ovarian cancer risk considering that initiation of ovarian cancer may have occurred many years before diagnosis; thus, dietary habits at a younger age were more important for disease development than recent diet. Finally, the follow-up time of this study was relatively short, and associations may need to be reconsidered after a longer follow-up period.

In summary, in the present study, we found no evidence of a linear inverse association between fruit and vegetable consumption and risk of ovarian cancer. However, a low consumption may increase the risk of ovarian cancer. The consumption of garlic/onion vegetables may exert a protective effect on ovarian cancer risk, but this observation needs to be confirmed in the future. Our findings regarding differential effects of fruit and vegetable consumption according to tumor histology warrant future investigations.

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