# Rheumatoid arthritis and cancer risk· results from the Greek European Prospective Investigation into Cancer and Nutrition cohort

Eleni Klinaki[1,2], Michail Katsoulis[1], Carlo La Vecchia[3] and Antonia Trichopoulou[1,4]

[1]Hellenic Health Foundation, Athens, Greece

[2]Second Department of Pediatrics, Athens University, "P. & A. Kyriakou" Children's Hospital, Athens, Greece

[3] Dept. of Clinical Sciences and Community Health, Università degli Studi di Milano

[4] Professor emeritus, National School of Public Health and University of Athens Medical School

Corresponding author:

Eleni Klinaki, MD

Kaisareias 13 & Alexandroupoleos

GR-115 27, Athens, Greece

Tel: +30 210 777 0697, Fax: +30 210 777 0771

e-mail: e.klinaki@hhf-greece.gr, eleni.t.klinaki@gmail.com

The work reported in the manuscript was completed without any financial support or other benefits from commercial sources and all of the authors listed have no financial interests, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

## Abstract

**Objective**: To investigate the relative risk of cancer development in rheumatoid arthritis (RA) patients in Greece, after taking into consideration treatment modalities.

**Methods**: The present analysis used data on medical history of 26 331 participants in the Greek arm of the European Prospective Investigation into Cancer and Nutrition (EPIC), that were collected at enrollment and thereafter during active follow-up. History of RA and of drug treatment for the disease, as reported at baseline examination, was linked to cases of cancer reported during follow-up

**Results**: A total of 91(9.9%) patients with RA developed a cancer, as compared with 1542 (6.1%) patients without RA. The overall HR of all cancers was 25% (95% CI: 1% - 54%) elevated among participants with prevalent RA, and almost all the site-specific incident cancer sites considered had rate ratios above unity. Regarding the contribution of RA medication, the HR of patients treated with salicylates was close to unity (1.07, 95% CI: 0.69-1.65), whereas those who were not treated with salicylates had a 31% (95% CI: 3% - 67%) increased risk for cancer incidence, compared to those without RA at baseline.

**Conclusions**: Ra patients have excess cancer risk due to either underlying complex disease pathways or treatment agents targeting immune function. Administration of salicylates appears to reduce the risk of developing malignancies.



## Key words

Rheymatoid arhtritis, cancer, EPIC study, salicylates, treatment

## Introduction

Inflammation plays a pivotal, yet inadequately quantified, role in the processes of carcinogenesis. In 1863, Virchow first suggested the linkage between inflammation and cancer. He hypothesized that the "lymphoreticular infiltrate" represents the origin of cancer at sites of chronic inflammation. His hypothesis was partly based on the observation that certain types of irritants, along with tissue injury and subsequent inflammation, enhance cell proliferation and therefore tumor growth [1]. In 1986, Dvorak described tumors as wounds that fail to heal. In fact, the tumor microenvironment shares many features with an inflammatory, chronic tissue damage. [2,3]. On the other hand, activation of inflammatory cells is considered to be part of an immune response of the body in order to eliminate mutant cells, a process called immunosurveillance, that was originally suggested by Ehrlich and later expanded and formalized [4].

Rheumatoid arthritis (RA) belongs in a group of chronic autoimmune-mediated and highly disabling diseases involving inappropriate or excessive immune responses accompanied by acute and chronic inflammation [5]. The risk of malignancies among RA patients has been of considerable interest due to the underlying pathophysiological mechanisms resulting in severe long-term inflammation. However, the association of malignancies with RA remains a field of controversy. Some studies have demonstrated a higher incidence of malignant diseases in patients with RA versus individuals in the general population. The relative risks (RR) in record linkage cohort studies from Taiwan [6] and Sweden [7-9] were 1.2 to 1.3 for all cancers combined, and there was some indication of excess risk for tobacco-related and skin cancer, though the associations with solid cancers were moderate and inconsistent across sites [8]. There was a strong association with lymphoid neoplasms,

and particularly with lymphomas, with RRs of the order of 2 to 3, though the issue is still open to clarification [6,10]. However, other reports have indicated an inconsistent or even lower risk of malignant diseases in patients with RA, particularly for colorectal, female-hormone related, and prostatic cancer [8-10].

Additionally, the therapy of RA may play a role towards cancer development which makes complex the interpretation of epidemiological results. Baecklund et al [6] suggested that chronic inflammation, rather than its treatment, is a major determinant of lymphoma risk in patients with RA. However, the wide usage of immunosuppressants drugs in order to achieve disease remission, supports the immunosurveillance hypothesis [9].

The aim of this study was to investigate the relative risk of malignant diseases, after the diagnosis of RA patients, in relation to treatment modalities, using a nationwide cohort database from Greece.

## Methods

The database used in the current analysis derived from the Greek arm of the European Prospective Investigation into Cancer and Nutrition (EPIC). The EPIC cohort consists of approximately 520 000 participants from 23 centers in 10 European countries. It provides data on health indicators and variables, dietary choices, lifestyle habits and socio-economic factors in relation to cancer and other chronic diseases. The design and methods of the EPIC study have been previously described [11].

The EPIC cohort in Greece comprises 28 572 volunteers (11 954 males and 16 618 females) aged 20 – 86 years whose enrollment took place between 1994 and 1999 from all over Greece. Since the baseline examination, participants are actively followed-up through telephone interviews conducted by specially trained health

professionals, every two to four years. Data from follow-up until the end of February of 2014 are considered. In particular, the present analysis is based on data collected from 26 331 study participants, after the exclusion of 2 241 subjects with prevalent cancer at recruitment or missing values for at least one of the study variables, or absence of follow-up. The procedures applied in the EPIC cohort were in accordance with the Declaration of Helsinki on the Ethical Principles for Medical Research involving Human Subjects of 1975, as revised in 1983. The study protocol was approved by the ethics committees of the International Agency for Research on Cancer (IARC) and the Medical School of the University of Athens. All study participants signed an informed consent form.

Exposure estimates and health outcomes

In the context of the EPIC study, detailed data on medical history of each participant were collected at enrollment and thereafter during active follow-up. For the present analysis, history of RA and of drug treatment for the disease, as reported during completion of the relevant questionnaire at baseline examination, were taken into consideration. The cases of RA refer to medically diagnosed conditions, that were self reported. The drugs reported were categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC). ATC codes referring to salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs) and biologic agents were used for the current study. The drugs included in the DMARDs category were: hydroxychloroquine, sulfasalazine, methotrexate, gold, d-penicillamine, azathioprine, cyclophosphamide, chlorambucil, cyclosporin, leflunomide, minocycline, tacrolimus [12-14].

The outcomes considered were cases of cancer with date of diagnosis subsequent to the date of entry to the study, i.e. reported during follow-up. In case of death, a next of kin was asked about further information and then the death certificate was identified in the respective registry, and the causes of death were recorded in the central database. The self-reported cancer incident and mortality cases were subsequently verified by reference to the medical records of the hospital where the subject had been diagnosed and/or treated. In our analysis, we included both verified (84%) and self-reported (16%) cases.

Statistical analysis

The participants personal characteristics were considered by sociodemographic, lifestyle and anthropometric variables evaluated at enrolment, separately for men and women. The overall and site-specific cancer distribution for subjects with and without RA at enrolment were also estimated.

For the evaluation of the relationship between RA and overall and site-specific cancer, Cox proportional hazards models were applied to derive multivariate hazard ratios (HR) and the corresponding 95% confidence intervals (CI), including terms for sex, age, height, tobacco and alcohol consumption, education, marital status and energy intake. Person-years were computed from baseline until the date of the participant's diagnosis for any cancer (for those who developed cancer during follow-up) or until the date of death (for those who died during follow-up, without any cancer) or until the date of the last follow-up.

All statistical analyses were conducted using the Stata/SE 11.0 for Windows statistical package (Stata CorpLP Lakeway Drive College Station, Texas, USA). Statistical significance was considered as two-sided $p<0.05$.

## Results

The baseline characteristics of the 26 331 study participants, in relation to sociodemographic, lifestyle and medical information are given in **Table 1**. The average age at enrollment of the subjects involved was 53.1 ± 12.6 years (range: 20 to 84 years), and 42% of the subjects were male. The prevalence of RA was higher in women (4.9%) compared to men (2.2%). The mean (SD) follow-up time was 10.8 (±3.7) years. During the observation period, a total of 1633 cancer cases were identified. Overall cancer incidence was higher in men than in women (7.2% vs 5.5% respectively).

An increased overall cancer proportion in patients with RA was observed when comparing the overall and site specific cancer incidence across the strata of participants with and without RA at baseline (**Supplementary data, Table 1)**. This finding was also apparent when applying Cox regression in order to estimate the HR among patients with RA for overall and site specific cancer incidence, adjusting for potential confounders (**Table 2**). The overall HR of all cancers was 25% (95% CI: 1% - 54%) elevated among participants with prevalent RA, and most of the site-specific incident cancer sites considered had rate ratios above unity. The higher HR in the present analyses were observed for urinary tract (HR=1.72), prostate (HR=1.62) and lung cancer (HR=1.53), albeit none of the estimated HRs was significant, due to the few cancer cases among participants with prevalent RA.

When the contribution of RA medication was investigated, the HR was 1.07 (95% CI 0.69-1.65) for patients treated with salicylates. Patients who were not treated with salicylates at enrollment had a 31% (95% CI: 3% - 67%) increased risk for cancer incidence, compared to those without RA at baseline (**Supplementary data, Table 2**). Among site-specific cancers, the difference according to treatment group was

apparently larger for digestive cancer cases, as the hazard ratio was elevated for those who did not receive salicylates at baseline [HR=1.40 (95% CI: 0.87 - 2.25)] and was below unity for those that received salicylates at baseline [HR=0.83 (95% CI: 0.31 - 2.22)] (data not shown in tables).

## Discussion

The present analysis, based on data from a prospective cohort of 26 331 men and women from different regions of Greece, demonstrated an increased cancer risk among RA patients, though no specific excess of lymphoid neoplasms. The elevated risk was apparent for overall cancer incidence, as well as for several cancer sites considered, after adjustment for potential confounders. While investigating the relationship between drug treatment of RA and neoplasia, administration of salicylates as part of RA medication appears to reduce the risk of developing malignancies. The beneficial effect of salicylates was observed for overall cancers, and was apparently greater for malignant neoplasms of the gastrointestinal tract.

Autoimmune diseases, like RA, have been considered to cause exaggerated and intolerant anti-self-tissue immune response, which appears to be responsible for the starting damage and the resulting chronic inflammation. This notion suggests an underlying disease-related cancer risk [6,15]. As far as lymphoid neoplasms are considered, there was only one case among patients with RA. Our findings, therefore, are little informative on the association between RA and lymphoid neoplasms, but remain compatible with the 2- to 3-fold excess risk reported in other studies, though the association remains unclear [6,10]. Moreover, a non significant heterogenetity was noted between the sexes, with higher risk among men than women. This may be due to a lower risk of female-hormone related cancers, as previously described [9,16].

For RA and other chronic inflammatory diseases subject to prolonged treatment with drugs that influence the immune function, it may be difficult to separate the effects of treatment from that of the disease itself. Most patients with RA are treated with more than one agent during their disease course and many studies, including the present, are based on populations treated with a variety of anti-inflammatory and immunosuppressive drugs. The latter are thought to favour cancer growth [9]. On the other hand, traditional treatment of RA includes salicylates, which may reduce the risk of cancer [17]. Salicylates affect mechanisms relevant to carcinogenesis, such as the inhibition of cyclo-oxygenase and subsequently prostaglandin production, the enhancement of cellular apoptosis and DNA mismatch repair, resulting to a possible protection against several cancers [16-20]. This is supported by the results of the present analysis, showing lower cancer risk for RA patients undertaking salicylates, though there was no significant heterogeneity.

The strengths of this study comprise the use of a prospective cohort that covers different regions of Greece and the long duration of the participants' monitoring through active follow-up. However, the overall association was of borderline significance, and the association of RA with selected site-specific cancers, such as urinary tract cancers, requires larger datasets to be adequately assessed.

Conclusions

Ra patients have excess cancer risk due to either underlying complex disease pathways or treatment agents targeting immune function. Over the last decades, great advances have been made in the field of clinical practice, since new and more effective drugs of the DMARDs category are tested and placed for broad usage. This dataset has not, however, adequate power to address this issue. In addition, it would

be advisable to reassess the risk-benefit balance of salicylates in RA patients for cancer prophylaxis, besides their benefits in vascular disease [17].

**Acknowledgements**

We would like to thank Professor Dimitrios Trichopoulos for his enlightening thinking and useful comments on this paper.

**References**

1. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; 420(6917): 860–867.

2. Arnold KM, Opdenaker LM, Flynn D et al. Wound Healing and Cancer Stem Cells: Inflammation as a Driver of Treatment Resistance in Breast Cancer. *Cancer Growth Metastasis* 2015; 8: 1-13.

3. Mantovani A. Cancer: Inflaming metastasis. *Nature* 2009; 457(7225): 36-7.

4. Shankaran V, Ikeda H, Bruce AT et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 2001; 410: 1107–1111.

5. Beyaert R1, Beaugerie L, Van Assche G et al. Cancer risk in immune-mediated inflammatory diseases (IMD). *Mol Cancer* 2013; 12(1): 98.

6. Chen YJ, Chang YT, Wang CB et al. The Risk of Cancer in Patients With Rheumatoid Arthritis: A Nationwide Cohort Study in Taiwan. *Arthritis Rheum* 2011; 63(2): 352-8.

7. Hemminki K, Li X, Sundquist K et al. Cancer risk in hospitalized rheumatoid arthritis patients. *Rheumatology* 2008; 47(5): 698-701.

8. Mercer LK, Davies R, Galloway JB et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. *Rheumatology* 2013; 52(1): 91-8.

9. Askling J, Fored CM, Brandt L et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64(10): 1421-6.

10. Smedby KE1, Askling J, Mariette X et al. Autoimmune and inflammatory disorders and risk of malignant lymphomas-an update. *J Intern Med* 2008; 264(6): 514-27.

11. 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(6B): 1113-24.

12. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the Management of Rheumatoid Arthritis: 2002 Update. *Arthritis Rheum* 2002; 46(2): 328-46.

13. Saag KG, Teng GG, Patkar NM et al. American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. *Arthritis Rheum* 2008; 59(6): 762-84.

14. Smolen JS, Landewé R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69(6): 964-75.

15. Franks AL, Slansky JE. Multiple Associations Between a Broad Spectrum of Autoimmune Diseases, Chronic Inflammatory Diseases and Cancer. *Anticancer Res* 2012; 32(4): 1119-36.

16. Terry MB, Gammon MD, Zhang FF et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA* 2004; 291(20): 2433-40.

17. Cuzick J, Thorat MA, Bosetti C et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol* 2015; 26(1): 47-57.

18. Smitten AL, Simon TA, Hochberg MC et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther* 2008; 10(2): R45.

19. Sutcliffe P, Connock M, Gurung T et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. *Health Technol Assess* 2013; 17(43): 1-253.

**20.** Elwood PC, Gallagher AM, Duthie GG et al. Aspirin, salicylates, and cancer. *Lancet* 2009; 373 (9671): 1301–09..

**Table 1:** Distribution of the 26331 study participants by sociodemographic, lifestyle and anthropometric variables evaluated at enrolment

| | **MEN** | **WOMEN** |
|---|---|---|
| **Age (in years)**, mean (sd) | 52.8 (12.8) | 53.3 (12.5) |
| **Height (in meters)**, mean (sd) | 1.70 (0.07) | 1.56 (0.07) |
| **BMI (in kg/m$^2$)**, mean (sd) | 28.2 (3.8) | 29.0 (5.2) |
| **Physical activity (in METS)**, mean (sd) | 35.3 (6.3) | 35.4 (4.3) |
| **Energy intake (in kcal/day)**, mean (sd) | 2333 (709) | 1866 (569) |
| **Alcohol intake (in gr/day)**, mean (sd) | 19.4 (25.8) | 3.5 (6.6) |
| **Education,** n (%) | | |
| ≤6 yrs | 6053 (55) | 10305 (67) |
| 7-12 yrs | 2710 (25) | 2744 (18) |
| >12 yrs | 2174 (20) | 2345 (15) |
| **Marital status,** n (%) | | |
| Married/live together | 9899 (91) | 12418 (81) |
| Alone/divorced/widowed | 1038 (9) | 2976 (19) |
| **Smoking status,** n (%) | | |
| Never | 2709 (25) | 11265 (73) |
| Former | 3686 (34) | 1173 (8) |
| Current | 4542 (42) | 2956 (19) |
| **Prevalent CVD,** n (%) | | |
| No | 9738 (89) | 14172 (92) |
| Yes | 1199 (11) | 1222 (8) |
| **Use of salicilates at baseline,** n (%) | | |

| | | |
|---|---|---|
| No | 9217(84) | 12925 (84) |
| Yes | 1720(16) | 2469(16) |
| **Rheumatoid arthritis at baseline,** n (%) | | |
| No | 10695 (98) | 14642 (95) |
| Yes | 242(2) | 752(5) |

**Table 2:** Hazard ratios from Cox regression of rheumatoid arthritis for overall and site specific cancer incidence, adjusted for potential confounders*

| | # of cancer cases | HR (95% C.I.) |
|---|---|---|
| **All cancers** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 1633 | 1.25 (1.01 - 1.54) |
| **Prostate cancer (men)** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 119 | 1.62 (0.71 - 3.70) |
| **Breast cancer (women)** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 294 | 1.08 (0.66 - 1.78) |
| **Digestive tract cancers** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 376 | 1.24 (0.81 - 1.92) |
| **Lung cancer** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 219 | 1.53 (0.85 - 2.76) |
| **Urinary tract cancers** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 129 | 1.72 (0.83 - 3.55) |
| **Lymphomas/ lymphoid neoplasms** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 19 | 0.97 (0.13 - 7.41) |
| **Other cancers** | | |
| Rheumatoid arthritis (vs no rheumatoid arthritis) | 477 | 1.15 (0.77 - 1.73) |

*potential confounders: age (in years; continuously), sex, height (in m; continuously), physical activity (in METS; continuously), energy intake (in kcal/d; continuously), alcohol intake (in gr/d; continuously), smoking status (never/former/current; categorically), education (<12 /12 />12 years of schooling; categorically), marital status (Married-live together / Alone-divorced-widowed; categorically)