Association between Echinococcus granulosus infection and cancer risk - a pilot study in Cyprus

<table>
<thead>
<tr>
<th>Journal:</th>
<th>International Journal of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>IJC-15-1244</td>
</tr>
<tr>
<td>Wiley - Manuscript type:</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>16-Jun-2015</td>
</tr>
</tbody>
</table>
| Complete List of Authors: | Oikonomopoulou, Katerina; Mount Sinai Hospital, Pathology and Laboratory Medicine  
Yu, Herbert; Cancer Epidemiology Program, University of Hawaii Cancer Center,  
Wang, Zhanwei; Cancer Epidemiology Program, University of Hawaii Cancer Center,  
Vasiliou, Stella K.; Mount Sinai Hospital, Pathology and Laboratory Medicine  
Brinc, Davor; University Health Network, Department of Clinical Biochemistry  
Christofi, Georgios; Ministry of Agriculture, Natural Resources and Environment, Department of Veterinary Services  
Theodorou, Marilena; European University,  
Pavlou, Pavlos; Ministry of Health, Health Monitoring Unit  
Hadjisavvas, Andreas; The Cyprus Institute of Neurology and Genetics, Department of Electron Microscopy/Molecular Pathology  
Demetriou, Christiana; The Cyprus Institute of Neurology and Genetics, Department of Electron Microscopy/Molecular Pathology  
Kyriacou, Kyriacos; The Cyprus Institute of Neurology and Genetics, Department of Electron Microscopy/Molecular Pathology  
Diamandis, Eleftherios; Mount Sinai Hospital, Department of Pathology and Laboratory Medicine; |
| Key Words:        | Echinococcus granulosus, cancer, infection |
Association between *Echinococcus granulosus* infection and cancer risk - a pilot study in Cyprus

Katerina Oikonomopoulou¹, Herbert Yu², Zhanwei Wang², Stella K. Vasiliou¹, Davor Brinc³, Georgios Christofi⁴, Marilena Theodorou⁵, Pavlos Pavlou⁶, Andreas Hadjisavvas⁷, Christiana Demetriou⁷, Kyriacos Kyriacou⁷, Eleftherios. P. Diamandis¹,³*

¹Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario M5T 3L9, Canada; ²Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu 96813, Hawaii, USA; ³Department of Clinical Biochemistry, University Health Network, Toronto, Ontario M5G 2C4, Canada; ⁴Department of Veterinary Services, Ministry of Agriculture, Natural Resources and Environment, Nicosia 1411, Cyprus; ⁵European University, Nicosia 1516, Cyprus; ⁶Health Monitoring Unit, Ministry of Health, Nicosia 1448, Cyprus; ⁷Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia 1683, Cyprus.

*Corresponding authors: Dr. Eleftherios P. Diamandis, Mount Sinai Hospital, Department of Pathology & Laboratory Medicine, 60 Murray Street, Room L6-201, Toronto, ON, M5T 3L9; Tel: (+1-416) 586-8443; Fax: (+1-416) 619-5521; E-mail: ediamandis@mtsain.on.ca; Dr. Kyriacos Kyriacou, Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, 6 International Airport Avenue, Agios Dometios, Nicosia 2370, P.O. Box 23462 / 1683, Cyprus; Tel: (+357) 22392631; Fax: (+357) 22392641; E-mail: kyriacos@cing.ac.cy.

**Brief description of novelty and impact**

Many infectious agents have been linked to cancer. The novel and salient finding of this work is that *Echinococcus granulosus* is positively-associated with cancer risk in contrast to previously reported data on a potential inverse and protective association between the *Echinococcus* parasite and cancer. In our study, the percentage of subjects that remained cancer-free decades post infection was significantly influenced from Echinococcus, evidence that support the role of many infectious agents on predisposing for carcinogenesis.

**Keywords**

*Echinococcus granulosus*; cancer; infection.

**Article category**

Research article (Infectious Causes of Cancer; Epidemiology)
ABSTRACT

Infections from microorganisms and parasites have been connected with either increased or decreased cancer risk. The objective of this study was to investigate whether *Echinococcus granulosus* (EG) infection is associated with cancer risk. We assembled a pilot retrospective cohort of patients who were diagnosed with EG in Cyprus between 1930 and 2011 using the EG registry records. Age- and gender-matched family members and neighbourhood controls without EG infection were selected as reference. Questionnaire information on personal data, medical history, and certain lifestyle factors was ascertained from each study subject through in-person interview. Cox proportional hazards regression analysis was performed to assess the association of EG infection and cancer risk. Individuals with EG infection (n=753) (n=249) were more likely to have cancer compared to those without EG infection, 11.65% versus 8.37% (p=0.0492). EG subjects were also more likely to drink alcohol, 26.51% versus 19.52% (p=0.0195), and have a family history of cancer, 49.80% versus 41.04% (p=0.0059). Survival analysis showed that compared to those without EG, subjects with prior EG infection had a higher risk for developing cancer. The hazards ratio (HR) was 1.595 (95% confidence interval between 1.008 and 2.525). The risk ratio did not change significantly (HR=1.536; 95%CI: 0.965-2.445) after adjusting for gender, year of birth, smoking status, alcohol drinking, and family history of cancer. Our study suggests that *Echinococcus granulosus* infection may increase cancer risk in the Cypriot population. If this observation can be confirmed independently, further investigation of the mechanisms underlying the association is warranted.
INTRODUCTION

Cancer remains a major health concern globally, despite significant advancements in early detection and effective treatment (1). Carcinogenesis is a multifactorial process, and infection and immunity play important roles in tumour development (2-4). Inflammation is now one of the well-recognized hallmarks of cancer (5;6) and immunological assessments have been suggested as an aid for a more optimal cancer classification in predicting prognosis (7;8). Infectious agents have been linked to a number of cancers, including hepatitis C or B virus with hepatocellular carcinoma (9), human papilloma virus with cervical cancer (10), *Helicobacter pylori* with gastric cancer (11), certain strains of *Escherichia coli* with colon cancer (12), and *Opisthorchis viverrini* or *Clonorchis sinensis* with cholangiocarcinoma (13;14). In addition, some disperse reports have suggested that microbes may also have a protective role against cancer; William Coley showed in the early 19th century that vaccination of sarcoma cancer patients with inactivated bacteria resulted in higher cure rates and more favourable progression (15;16). In another example, BCG vaccine, an attenuated form of *Mycobacterium bovis*, is now an FDA-approved agent for the first-line intravesical treatment of bladder cancer (17-19).

Amongst the immunoregulatory microbes, parasitic worms such as helminths have generally attracted attention as potential infectious factors that can influence immunity while at the same time successfully adapt to their host environment in a commensal or tolerable parasitic fashion (20;21). The platyhelminth, *Echinococcus granulosus* (EG), is a parasite that is highly endemic in regions of South Africa, America and the Mediterranean basin (22-25). While its life cycle is largely dependent on sheep and dogs, human infections occur upon oral ingestion of EG eggs which result in subsequent formation of parasitic cysts in various tissues. Humans are dead-end hosts of EG, and may develop symptoms of EG infection, depending on the position and size of the parasitic cysts. Some cysts may remain undetected for many decades. The sustained EG infection may have effects on the host innate and...
adaptive immunity, such as changing the dominance of Th1-type versus Th2-type immunity, triggering the activation of regulatory T cells (Tregs), releasing highly-immunogenic antigens, such as antigens B and T/Tn, and inducing the production of specific antibodies, i.e. IgG, IgM and IgE (26-29). The infection-triggered immune changes can, in principle, affect the host response to carcinogenesis, for example as a result of common antigenicity or regulation of host immune response (reviewed by (30;31)). A recent observational study reported that the prevalence of *E. granulosus* infections in patients with solid tumours was substantially lower than those in non-cancer patients with traumas, and that tumours in infected patients were also significantly less frequent than those in uninfected subjects (32). *E. granulosus* components were further reported to inhibit proliferation and promote lysis of fibrosarcoma and baby hamster kidney cells *in vitro* (33).

To evaluate the observations of these reports and to address the association of EG infection and cancer risk in more detail, we established a pilot retrospective cohort of people with and without *E. granulosus* infection in Cyprus and compared their cancer incidences using the Cox proportional hazards regression analysis.
MATERIALS AND METHODS

Ethics Approval

The study was approved by the National Bioethics Committee of Cyprus (where the study population was located), as well as the Research Ethics Board of Mount Sinai Hospital in Canada (where the Principal Investigator’s laboratory is located).

Study participants

Echinococcus patients: *E. granulosus* infection was a major health concern in Cyprus between 1960 and 1975 (34;35). To control the spread of the disease, the government established an Echinococcus registry that contained more than 800 Caucasian patients with confirmed diagnosis of Echinococcus granulosus infection. These patients, were infected between 1926 and 1991 throughout Cyprus (36). The registry contained information on last known residence and some information on Echinococcus clinical/laboratory findings or disease characteristics, i.e., date of diagnosis, clinical manifestation, date and type of treatment, outcome of disease.

Non-infected controls: For each patient, one gender- and age-matched (±14 years) relative and two gender- and age-matched (±5 years) neighbours without EG infection were recruited as controls. In cases where relative controls could not be found, a third neighbourhood control was recruited instead (three neighbourhood controls). If a relative control was more than 5 years older or younger than the matched case, an additional neighbourhood control was recruited for that case (i.e., the case had one relative control and three neighbourhood controls). If a case had more than one eligible relative controls, we randomly selected one, regardless of their cancer diagnosis or vital status (alive or dead). For multiple neighbourhood controls, we selected the closest available neighbours regardless of their cancer diagnosis or vital status.
Other consideration for participant selection: For identified study subjects who had emigrated or were deceased, demented or unable to communicate/recollect at the time of the study, a family member was invited as a proxy, provided that sufficient medical information was known. Number of proxies was 100 for EG patients and 194 for non-EG control subjects. We elected to include all subjects who fulfilled the recruitment criteria, regardless of whether they were alive or deceased at the time of the interview. With this strategy, bias towards selection of alive participants was minimized. To minimize recall bias, we evaluated the subject's ability to recall by asking them personal and family information (such as age, name, contact information, family history, medical history etc) and by comparing the information provided to details available in the Echinococcus governmental registry (when applicable) or to other medical records (when available).

Subject contact and interviewing

A letter of introduction, a consent form and a questionnaire were provided to all the subjects in preparation for interview. The questionnaire collected: (a) contact information; (b) personal information, such as date of birth, profession, date and cause of death (when applicable), current weight and height; (c) details on Echinococcus infection; (d) history of cancer; (e) family history of cancer; (f) smoking habits and alcohol consumption.

Data analyses

Chi-square test was used to compare the differences of gender, year of birth, lifestyle factors, medical history, and family history of cancer between EG patients and controls. The association between EG infection and cancer risk was analyzed using the Cox proportional hazards regression model. In the Cox regression analysis, time course (or survival time) was defined by the following conditions. The starting time point was the date of EG diagnosis for EG patients or a date similar to the diagnostic date...
of their matched EG cases for the controls. The end point was the date of cancer diagnosis, date of
death, or date of study completion if alive and no cancer diagnosis. Subjects who died during the
follow up time were considered censored. A univariate model was constructed first to assess the
association of EG infection with cancer risk. After univariate analysis, multivariate regression models
were developed to adjust for confounding factors which included gender, year of birth, smoking status,
alcohol drinking, and family history of cancer.
RESULTS

Study enrolment

Multiple entries of the same patient in the Cypriot governmental Echinococcus registry, which referred
to errors or to more than one surgery performed at the same patient and recorded at different times,
were considered as a single entry. This approach resulted in a database of 726 entries of subjects
diagnosed with Echinococcus infection. We sought the present address of each of these formerly-
infected patients and/or their surviving relatives with the help of local public and community
authorities. Several of these subjects could not be located due to immigration, errors in the registry, or
lack of survived or identified family members.

We were thus able to locate about 57% of the registered EG patients in the government records. The
participation rate within this population was about 75%, while 20% was found to consist of multiple
entries in the registry (e.g. a patient using two different names at database registration).

New cases, not originally included in the Echinococcus registry, were identified from the general
population (cases voluntarily identified themselves) during our public informational seminars and were
invited to participate in our study. After excluding participants whose questionnaire information was
missing or unreliable, we enrolled a total of 249 subjects who were formerly diagnosed with EG
infection in our study. These former EG patients presently resided in the following prefectures of
Cyprus: Nicosia, Larnaca, Limassol, Paphos, and Ammochostos. Family controls were enrolled for 143
out of the 249 former Echinococcus patients and the remaining were neighbourhood controls (n=610).

Distributions of study factors

Table 1 shows the distributions of study factors between EG cases and their matched controls. As
anticipated, the matched factors, gender and year of birth were not different between cases and
controls. However, we did find that patients with former infection of *Echinococcus granulosus* were more likely to be diagnosed with cancer compared to their controls, 11.65% versus 8.37%. (p=0.0492).

EG subjects were also more likely to drink alcohol, 26.51% versus 19.52% (p=0.0195) and to have a family history of cancer, 49.80% versus 41.04% (p=0.0059).

**Kaplan-Meier analysis**

The results of the Kaplan-Meier survival analysis, i.e. the time to develop cancer, are shown in Figure 1. These data indicated that formerly-infected by *Echinococcus granulosus* subjects were more likely to develop cancer compared to non-infected subjects (p=0.045).

**Cox regression analysis**

Results of Cox regression analysis are shown in Table 2. Univariate analysis suggested that EG infection was associated with increased risk of cancer; the hazard ratio was 1.595, 95% confidence interval was between 1.008 and 2.525. This finding was consistent with the observation of different rates of cancer diagnosis between subjects with and without EG shown in Table 1. The hazards ratio did not change substantially (HR=1.536; 95%CI: 0.965-2.445) after gender, year of birth, smoking status, alcohol drinking, and family history of cancer were adjusted in the analysis. Specifically, individuals with former infection of EG had 53.6% higher risk to develop cancer compared to those without history of EG infection.
DISCUSSION

This study aimed to evaluate cancer risk in association with previous infection by *Echinococcus granulosus*. For this purpose we retrospectively collected medical information from former *Echinococcus* Cypriot patients or their families. The confined environment of Cyprus, the organized and nearly complete collection of information by a significant number of pre-existing *Echinococcus* patients, and the current almost-complete eradication of infection in the island were optimal factors that facilitated our study and ensured the homogeneity of our study population. The small size of the island also eased our access to every participant location. The main finding of this pilot study is that infection by *Echinococcus granulosus* influences the risk for carcinogenesis in a way different than the one previously hypothesized. More specifically, our results revealed a positive association of the parasitic infection with cancer, similar to that of *E. coli* and colorectal carcinoma (12;37). Our finding is in disagreement with the two previous studies in which subjects with *E. granulosus* infection showed a lower prevalence of cancer (1 cancer in 1000 infected patients) and fewer cancer patients reported *Echinococcus* infection (2 infections out of 2086 cancer patients as opposed to 7 out of 350 trauma patients; 1 infection out of 1200 hematologic malignancy patients) (32;38). Our study suggests that cancer risk may increase decades after *Echinococcus* diagnosis, indicating a possible involvement of chronic inflammation in carcinogenesis. In contrast, the previous reports investigated the presence of *Echinococcus* at the time of cancer diagnosis (32;38) or the presence of cancer at the time of diagnosis of *Echinococcus granulosus* (32). This type of study design does not consider the appropriate post-infection latency that would allow cancer to develop, and may thus underestimate the actual number of cancer cases. In our cohort we only had 3 cases who reported coexistent infection and cancer out of the 249 patients surveyed, while the importance of cancer diagnosis many decades post *Echinococcus* infection became obvious in our survival analysis depicted in Figure 1 that demonstrated significant
differential increase in cancer cases beyond 60 years post EG diagnosis. It is also not clear whether age stratification or matching was used in those previous studies. If the age parameter was overlooked, cancer risk would be underestimated due to studying younger populations or due to age differences between subjects with or without EG infection. In addition, the previous work may have not used appropriate controls with regard to their comparability to the patients group. This issue is of importance and requires special consideration, given that 60% of Echinococcus cases can remain asymptomatic for many years (39). In our study we considered the inclusion of at least three control subjects per Echinococcus disease patient and acquired a lengthy retrospective follow-up time to ensure that cross-contamination level would remain lower than 10%, an estimated number based on prevalence of the infectious disease during 1960-1985 in Cyprus.

Our finding was also inconsistent with a previous in vitro study which observed decreased proliferation of cancer cells treated with parasitic extracts (33), an indication of potential protective Echinococcus effects against cancer, which has not, however, been shown in vivo. Interestingly, one of the most immunogenic helminthic components, the T/Tn antigen (also known as the Thomsen-Friedenreich antigen), which is present in *E. granulosus*, is shared by many types of tumours (40-42) and is expressed more frequently in patients with less extensive malignancy (42). Expression of this common tumour-parasite T/Tn antigen varies among tumour types/sites (41-44); it is also expressed in normal tissues at lower levels compared to malignant cells (45). Despite the non-specific expression of T/Tn antigen, vaccination regimens based on T/Tn have shown potential value to prevent breast cancer recurrence that has not yet been proven of significant value for clinical practice (46). These observations suggest a potential anti-carcinogenic role of the helminthic infection which cannot be extrapolated from our study.

It is noteworthy that our study design did not evaluate the potential specific role for Echinococcus immunogenic components against antigenically-related tumours. The Echinococcus parasite may
coincide with tumour cells, as it has been previously shown (32;47). In principle, such a co-existence

can influence the antigenically-similar tumour cell ability to thrive in the human host and, thus, the
development or outcome of cancer, an interesting possibility that could not be studied in our cohort
design due to lack of detailed cancer biological, diagnostic and progression/survival data.

In addition, it is possible that *Echinococcus granulosus* exerts effects that are cancer type-specific and
not systemic. Given the small number of cancer patients involved in our study, this issue could not be
addressed; we, however, observed that the 4 most common cancer types in our cohort were: colon,
skin, breast, prostate for EG patients and prostate, breast, skin, lung for non-EG patients. It is further
possible that the parasitic infection influences tumourigenesis in a time-specific manner, i.e. by
influencing the disease progression/prognosis or by signalling earlier/later manifestation of symptoms
or by triggering rapid/slower tumour growth and metastasis. A recent work considered the above
hypotheses, reporting that *E. granulosus* infection can favour concurrent liver metastasis by influencing
Th1 immune response in a murine model of infection and cancer (48). In our study, even though the
survival analysis pointed to a marginally-more unfavourable cancer survival in Echinococcus patients,
the number of cases available in our cohort would not allow more detailed conclusions towards such a
specific effect.

A cohort that includes a larger study population in countries with currently active Echinococciosis
should be investigated prospectively in order to ensure sufficient power for inclusion of patients with
many cancer types and availability of detailed medical and biological/biochemical information for
Echinococcus (e.g. active or inactive parasitic cyst, type of treatment, site), cancer (type of treatment,
site, type of tumour, outcome), and confounding pathophysiological factors during the timeframe of the
study. Specifically the issue of type and length of treatment received may, in principle, have
significance for the outcome of such a study in two ways: (a) an inactive non-treated Echinococcus cyst
may still exert effects on host pro- or anti-carcinogenic immune responses; (b) compounds used for the
treatment of active parasitic cysts may directly influence the development of carcinogenesis. Our lengthy retrospective timeframe did not allow having access to detailed medical records related to our patients, a limitation that restricted us in receiving several pieces of information that would have otherwise be very important in a more detailed and stratified analyses.
ACKNOWLEDGEMENTS

This work was supported by an Internal Research Fund from the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada (EPD). No Potential Conflicts of Interest are reported, and the funding agency played no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication. We would like to extend a warm thanks to all subjects who volunteered to participate in our study. We also thank staff members of the Cypriot Ministry of Health, Ministry of Agriculture, Natural Resources and Environment and Government Registry offices for providing assistance with administration and data collection. We further gratefully acknowledge the staff members at county level, prefecture level, and region level, as well as our colleagues and volunteers in Cyprus that provided assistance with informing potential participants and with field investigation, administration, and data collection. We would also like to thank Fivi Stavrou, Rea Anastasiou, Aliki Anastasiou, Christia Mallouri, Maria Papadopoulou, Chrysostomos Meli (The Cyprus Institute of Neurology and Genetics, Cyprus) for forming our patient recruitment team, Dr. Ana Konvalinka (Mount Sinai Hospital, Canada) for offering consultation on medical history categorization, and Apostolos Dimitromanolakis (Mount Sinai Hospital, Canada) for additional data analyses.
REFERENCES


### TABLES

**Table 1. Description of study variables in former *Echinococcus granulosus* (EG) patients and controls.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Variable</th>
<th>Non-EG (n=753) No. (%)</th>
<th>EG (n=249) No. (%)</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>388 (51.53)</td>
<td>127 (51.00)</td>
<td>0.8861</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>365 (48.47)</td>
<td>122 (49.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Birth year</strong></td>
<td>&lt;1940</td>
<td>374 (49.67)</td>
<td>127 (51.00)</td>
<td>0.7147</td>
</tr>
<tr>
<td></td>
<td>≥1940</td>
<td>379 (50.33)</td>
<td>122 (49.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>No</td>
<td>685 (90.97)</td>
<td>215 (86.35)</td>
<td>0.0492</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>63 (8.37)</td>
<td>29 (11.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unsure</td>
<td>5 (0.66)</td>
<td>5 (2.01)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>No</td>
<td>617 (81.94)</td>
<td>204 (81.93)</td>
<td>0.9968</td>
</tr>
<tr>
<td></td>
<td>(≥1 cigarettes daily for the past 6 months)</td>
<td>Yes</td>
<td>136 (18.06)</td>
<td>45 (18.07)</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>No</td>
<td>606 (80.48)</td>
<td>183 (73.49)</td>
<td>0.0195</td>
</tr>
<tr>
<td></td>
<td>(≥1 glasses weekly for the past 6 months)</td>
<td>Yes</td>
<td>147 (19.52)</td>
<td>66 (26.51)</td>
</tr>
<tr>
<td><strong>Family cancer history</strong></td>
<td>No</td>
<td>431 (57.24)</td>
<td>116 (46.59)</td>
<td>0.0059</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>309 (41.04)</td>
<td>124 (49.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unsure</td>
<td>13 (1.73)</td>
<td>9 (3.61)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. The association of former infection by *Echinococcus granulosus* (EG) with cancer risk in different models.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects No. (%)</th>
<th>Cancer outcome No. (%)</th>
<th>Log-rank P</th>
<th>HR(^1)</th>
<th>95% CI(^2)</th>
<th>HR(^1)*</th>
<th>95% CI(^2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-EG</td>
<td>729 (92.87)</td>
<td>56 (7.13)</td>
<td>0.0445</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>EG</td>
<td>237 (89.77)</td>
<td>27 (10.23)</td>
<td></td>
<td>1.595</td>
<td>1.008 2.525</td>
<td>1.536 0.965</td>
<td>2.445</td>
</tr>
</tbody>
</table>

*adjusted for gender, year of birth, smoking, alcohol, family cancer history.

\(^1\)HR, hazards ratio  
\(^2\)CI, confidence interval
FIGURE LEGEND

Figure 1. Cancer diagnosis in patients formerly infected by *Echinococcus granulosus* and controls. The x-axis indicates the follow-up time since *Echinococcus granulosus* (EG) diagnosis for cases (EG) or a similar time for the respective controls (non-EG) of each case. The y-axis indicates the percentage of participants (EG cases or controls) that remain cancer-free at a given time.
Figure 1. Cancer diagnosis in patients formerly infected by Echinococcus granulosus and controls. The x-axis indicates the follow-up time since Echinococcus granulosus (EG) diagnosis for cases (EG) or a similar time for the respective controls (non-EG) of each case. The y-axis indicates the percentage of participants (EG cases or controls) that remain cancer-free at a given time.

187x136mm (300 x 300 DPI)