ARTICLE
Epidemiology

Syncope as a sign of occult cancers: a population-based cohort study

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BACKGROUND: We examined if syncope was a marker of an occult cancer by comparing the risk in patients with a syncope episode with that of the general population.

METHODS: Using Danish population-based medical registries, we identified all patients diagnosed with syncope during 1994–2013 and followed them until a cancer diagnosis, emigration, death or end of follow-up, whichever came first. We computed cumulative risks and standardised incidence ratios (SIR) with 95% confidence intervals (CI).

RESULTS: Among 208,361 patients with syncope, 20,278 subsequent cancers were observed. The 6-month cumulative risk of any cancer was 1.2%, increasing to 17.9% for 1–20 years of follow-up. The highest cumulative risks after 6 months of follow-up were lung cancer (0.2%), colorectal cancer (0.2%), prostate cancer (0.1%) and brain cancer (0.1%). The 6-month SIR were 2.7 (95% CI: 2.4–3.0) for lung cancer, 2.0 (95% CI: 1.8–2.2) for colorectal cancer, 1.7 (95% CI: 1.5–1.9) for prostate cancer and 10.0 (95% CI: 8.6–11.4) for brain cancer.

CONCLUSIONS: Syncope was a weak marker of an occult cancer. In short-term the highest cumulative risks were observed for lung, colorectal, prostate and brain cancers. An aggressive search for occult cancer in a patient with syncope is probably not warranted.

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BACKGROUND
Syncope is defined as a sudden loss of consciousness of short duration, with an inability to maintain postural tone, and spontaneous complete recovery.1–2 Episodic occurrence occurs frequently, accounting for ~1% of all referrals to emergency departments.1 The lifetime cumulative risk of syncope is approximately 35%.3 Clinically, the condition is categorised on the basis of underlying pathophysiology, i.e. reflex-mediated, orthostatic hypotension or cardiac syncope.1 Whether syncope may be the presenting sign of an occult cancer is largely unknown. Only a few case reports are available.4–17 Thus, firm epidemiological evidence on the association between syncope and cancer is lacking.

Syncope can occur due to stimulus of the parasympathetic nervous system or carotid sinus by direct neoplastic infiltration.7,9–16 Syncope also can be the first sign of intracranial tumours due to involvement of autonomic cardiovascular control areas.18–20 Additionally, a recent multicentre study showed that pulmonary embolism was identified in nearly one of every six patients hospitalised for a first episode of syncope,21 and pulmonary embolism, in turn, is established as a marker for occult cancer.22–23 Therefore, it is possible that syncope may be associated with an underlying undiagnosed cancer. Electrolyte imbalance and paraneoplastic phenomena also may induce syncope, as observed in patients with pheochromocytoma,24 mastocytosis,25,26 and carcinoid syndrome.27 To study these issues in detail, we examined overall risk of cancer and risk of site-specific cancers in a large cohort of syncope patients, and we compared their cancer risk with that of the general population.

METHODS
Design and setting
We conducted a nationwide population-based cohort study in Denmark between 1 January 1994 and 30 November 2013. The Danish national health system provides tax-supported healthcare to all residents of Denmark, ensuring equal access to general practice and hospital care.28 Contacts with the healthcare system are recorded in national databases.29,30 Linkage among databases is possible through a unique ten-digit personal identification number assigned to each Danish resident.29

Patients with syncope
We used the Danish National Patient Registry (DNPR) to identify all patients with a first-time inpatient, outpatient or emergency room diagnosis of syncope. We excluded patients with a history of a cancer diagnosis recorded in the Danish Cancer Registry (DCR). The DNPR contains data on all inpatient admissions to non-psychiatric hospitals since 1977 and on hospital outpatient and emergency room contacts since 1995. Information recorded in the DNPR includes admission and discharge dates, and one primary and up to nineteen secondary discharge diagnoses coded according to the International Classification of Diseases (ICD) Tenth Revision since 1994.30 The syncope diagnosis has previously
been reported with a positive predictive value of 95%, and thus diagnostic misclassification of the exposure is likely negligible.\textsuperscript{33}

Cancer
To obtain information on incident cancers diagnosed after a syncope episode, we linked our patient cohort to the DCR.\textsuperscript{32} This registry contains detailed information on cancers diagnosed in Denmark since 1943, with information on morphology, histology and cancer stage at diagnosis.\textsuperscript{33} We categorised the cancers according to recommendations from the Danish National Board of Health\textsuperscript{34} (Supplementary Table 1).

Comorbidity
Information on several comorbidities was obtained from the DNPR. These included diagnoses of head trauma, diabetes mellitus, myocardial infarction, heart failure, atrial fibrillation, valvular heart disease, chronic lower respiratory diseases, chronic kidney disease, obesity, alcoholism-related disorders, epilepsy, narcolepsy and cataplexy, stroke, angina pectoris, hypertension, anaemia, lower urinary tract obstruction and venous thromboembolism. Changes in vital and migration status were ascertained from the Danish Civil Registration System, which is electronically updated on a daily basis.\textsuperscript{45} All ICD codes used in the study are provided in Supplementary Table 1.

Statistical analyses
We followed the patients from their syncope episode (hospital contact date) until a cancer diagnosis, death, emigration, or 30 November 2013, whichever came first. We tabulated characteristics of the syncope cohort and calculated cumulative risks (%) of a cancer diagnosis during 0–6 months, >6–12 months and 1–20 years following a syncope episode, treating death as a competing risk.\textsuperscript{35,36} Assuming that the observed number of cancers followed a Poisson distribution, we calculated relative risks by comparing the observed number of cancers (based on national incidence rates, by sex, age and calendar year, in 1 year intervals) to obtain a standardised incidence rate (SIR) with 95% confidence intervals (CIs). The SIR analysis also takes into account the competing risk of death, as individuals are censored when they die and because the national cancer incidence rates are based exclusively on individuals at risk of cancer, censoring individuals who die or emigrate. Exact 95% CIs were used when the observed number of cancers was less than ten.\textsuperscript{35,37} We stratified the main analyses (SIRs) by follow-up time (0–6 months, >6–12 months, >12 months and 0–20 years), age (0–29 years, 30–49 years, 50–69 years and 70 years), calendar period (1994–1998, 1999–2003, 2004–2008 and 2009–2013) and sex. In addition, we stratified the analyses by presence or absence of the individual comorbidities presented in Table 1 (except for narcolepsy and cataplexy, due to their low prevalence). This analysis was performed only for the four most common cancers to retain statistical precision of the estimates (Supplementary Table 2–5). We calculated the number of patients needed to be screened to find 1 excess cancer as the reciprocal of excess risk, assuming that the cancer diagnosed within 6 months after the syncope diagnosis was already present at the syncope diagnosis.

All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08). In Denmark, registry-based research does not require permission from an ethics committee or informed consent from patients.

RESULTS
We identified 208,361 patients with a first-time episode of syncope. Among these patients, 47% were male, 88% had syncope as their primary reason for the index hospital contact. In the syncope cohort, 50% were inpatients, 13% outpatients and 37% emergency room contacts. The median age was 57 years and median follow-up time was 5.6 years. Head trauma, cardiovascular disease (hypertension, atrial fibrillation and angina pectoris) and chronic lower respiratory diseases were the most frequent comorbidities (Table 1).

We observed 20,278 cancers during 20 years of follow-up. The cumulative risk of any cancer diagnosis after 6 months of follow-up was 1.2%, increasing to 17.9% for 1–20 years of follow-up (Table 2). The 6-month cumulative risk of cancer was mainly driven

| Table 1. Characteristics of the syncope cohort, Denmark, 1994–2013. |
|-------------------|------------------|------------------|------------------|
| Total number      | 208,361 (100)    |                  |                  |
| Sex               |                  | Male             | Female           |
|                   |                  | 97,135 (47)      | 111,226 (53)     |
| Type of contact   |                  |                  |                  |
| Inpatients        | 104,420 (50)     |                  |                  |
| Outpatients       | 27,427 (13)      |                  |                  |
| Emergency patients| 76,514 (37)      |                  |                  |
| Type of diagnosis |                  |                  |                  |
| Primary diagnosis*| 182,869 (88)     |                  |                  |
| Secondary diagnosis| 25,492 (12)   |                  |                  |
| Median age, years (25th–75th percentiles) | 57 (32–74) |                  |                  |
| Age group, years  |                  |                  |                  |
| 0–29 years        | 48,143 (23)      |                  |                  |
| 30–49 years       | 38,257 (18)      |                  |                  |
| 50–69 years       | 56,731 (27)      |                  |                  |
| ≥70 years         | 65,230 (31)      |                  |                  |
| Calendar period   |                  |                  |                  |
| 1994–1998         | 39,622 (19)      |                  |                  |
| 1999–2003         | 51,815 (25)      |                  |                  |
| 2004–2008         | 56,501 (27)      |                  |                  |
| 2009–2013         | 60,423 (29)      |                  |                  |
| Median follow-up time, years (25th–75th percentiles) | 56 (2–10) |                  |                  |
| Comorbidities     |                  |                  |                  |
| Head trauma       | 58,958 (28)      |                  |                  |
| Diabetes mellitus | 11,484 (6)       |                  |                  |
| Myocardial infarction | 12,869 (6)    |                  |                  |
| Heart failure     | 11,400 (6)       |                  |                  |
| Atrial fibrillation| 17,637 (8)      |                  |                  |
| Valvular heart disease | 4903 (2)     |                  |                  |
| Chronic lower respiratory diseases | 15,805 (8) |                  |                  |
| Chronic kidney disease | 3961 (2)      |                  |                  |
| Obesity           | 6457 (3)         |                  |                  |
| Alcoholism-related disorders | 10,309 (5)   |                  |                  |
| Epilepsy          | 10,093 (5)       |                  |                  |
| Narcolepsy and cataplexy | 48 (0)       |                  |                  |
| Stroke            | 14,829 (7)       |                  |                  |
| Angina pectoris   | 18,287 (9)       |                  |                  |
| Hypertension      | 26,771 (13)      |                  |                  |
| Anemia            | 2171 (1)         |                  |                  |
| Lower urinary tract obstruction | 5387 (3)     |                  |                  |
| Venous thromboembolism | 4986 (2)      |                  |                  |

Patients also can be assigned one or more appropriate secondary diagnoses. *Primary diagnosis refer to the primary reason for a hospital contact
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In this large population-based cohort study, syncope was a weak marker of an occult cancer. The cumulative risks were low and after 6 months of follow-up, it was mostly elevated for lung, colorectal, prostate and brain cancers.

The association between syncope as marker of occult cancer has been sparsely documented in the literature. Several case reports found that syncope was the presenting symptom of lung cancer and brain cancer. In contrast, such reports were not found for colorectal or prostate cancers. This may indicate that cancer-induced syncope is more frequently due to undiagnosed lung cancer than colorectal or prostate cancer. Our findings suggest that the cumulative risks were low for these conditions.
Cancer might be associated with syncope for several pathophysiologic reasons. Brain cancer may cause syncope due to cerebral hypoperfusion or brain metastases. Cerebral hypoperfusion may be induced by compression of blood vessels by tumours, reducing blood flow to the heart or brain, or by direct infiltration of the vagus and glossopharyngeal nerves. Although the mechanisms are not well understood, brain metastases from lung cancer may involve areas responsible for cardiovascular control (brainstem, thalamus, hypothalamus, insular cortex or amygdala) and thus cause syncope.\textsuperscript{4,42,43} This is supported by case reports of frontal and temporal lobe tumours, as well as craniocervical junction tumours, which provide the best explanation for bradycardia and/or cardiac asystole and subsequent syncope.\textsuperscript{18–20} It is also possible that invasion or compression of vessels by a tumour reduce blood flow to the heart and brain, inducing cerebral hypotension. However, only one case report on infradiaphragmatic tumours in the form of renal cell carcinoma has supported this explanation.\textsuperscript{8} Another possibility is metastases from a colorectal cancer to the lung and brain; however, this is not a frequent complication.\textsuperscript{44,45} Furthermore, anaemia may play a role in inducing syncope,\textsuperscript{46} and is often a complication to cancer.\textsuperscript{27} This notion was supported by our stratified analyses, although the prevalence of anaemia likely is underestimated in our population. This misclassification implies that the impact of anaemia might be even higher than observed in our data. Another well-known syncope-inducing mechanism is micturition,\textsuperscript{49} venous thromboembolism, suggesting that venous thromboembolism...
may play a minor role only in the association between syncope and cancer.

As documented in our analyses, syncope may be the first sign of some cancers. Occult cancer diagnosed at the short-term follow-up following syncope likely represent aggressive and fast-growing tumours (i.e. lung cancer and colorectal), or slow-growing tumours that have gradually become large, until a certain point, where they will facilitate a syncope episode. As discussed previously it could involve e.g. the lower urinary system, compression of blood vessels to the heart and brain, or a slowly evolving anaemia.

At long-term follow-up, the predominant cancers are most likely slow-growing tumours (e.g. carcinoid tumours) that have been present for years without noticeable symptoms. At one point, they may hemodynamically destabilise the patient and induce a syncope.

The main strength of our study is its nationwide population-based cohort design within a setting of free and equal access to healthcare service, which limits selection and referral biases. Our study also has several potential limitations. Heightened diagnostic effort may explain in part the 6 months as a compensatory delay. Heightened diagnostic effort may explain in part the increased incidence of syncope.

In this population-based study, an episode of syncope was a weak marker of an occult cancer diagnosed within the following 6 months, mainly driven by lung, colorectal, prostate and brain cancers.

CONCLUSION
In this population-based study, an episode of syncope was a weak marker of an occult cancer diagnosed within the following 6 months, mainly driven by lung, colorectal, prostate and brain cancers.

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AUTHOR CONTRIBUTIONS
M.O.B.L. wrote the manuscript with support from K.A. and J.S. H.T.S conceived the presented idea, designed the study, and supervised the findings. D.K.F. did the statistical analysis and modelling. All authors discussed the results and contributed to the final manuscript.

ADDITIONAL INFORMATION
Ethics approval and consent to participate In Denmark, registry-based research does not require permission from an ethics committee or informed consent from patients.
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19. Park, K., Her, S., Lee, J., Yoon, H., Chin, J., Jeon, J., Park, Y., Do, K., Jung, Y. & jin, S. Brain tumor is a rare cause of both bradycardia and seizure. Korean J Soc. Circulation. 37, 449–452 (2007).

20. Champagne, P. O. & Boyanova, M. W. Cranio-cervical junction meningioma without hydrocephalus presenting solely with syncope: Report of 2 Cases. World Neurosurg. 114, 161–164 (2018).

21. Prandoni, P., Lensing, A. W., Prins, M. H., Giamiachella, M., Perlati, M., Mumoli, N. et al. Prevalence of pulmonary embolism among patients hospitalized for syncope. N. Engl. J. Med. 375, 1524–1531 (2016).

22. Monreal, M., Casals, A., Boix, J., Olazabal, A., Montserrat, E. & Mundo, M. R. Occult cancer in patients with acute pulmonary embolism. A prospective study. Chest 103, 816–819 (1993).

23. Monreal, M., Lensing, A. W., Prins, M. H., Bonet, M., Fernandez-Llamazares, J., Muchart, J. et al. Screening for occult cancer in patients with acute deep vein thrombosis or pulmonary embolism. J. Thrombosis Haemost. 2, 876–881 (2004).

24. Roshan, J., George, O. K., Vineet, S., George, P. V. & Jose, V. J. Torsade de pointes in a case of pheochromocytoma-an unusual presentation of an uncommon disease. Indian Heart J. 56, 248–249 (2004).

25. Shaffer, H. C., Parsons, D. J., Peden, D. B. & Morrell, D. Recurrent syncope and anaphylaxis as presentation of systemic mastocytosis in a pediatric patient: case report and literature review. J. Am. Acad. Dermatol. 54(S Suppl), S210–S213 (2006).

26. Bains, S. N. & Hsieh, F. H. Current approaches to the diagnosis and treatment of systemic mastocytosis. Ann. Allergy, Asthma Immunol. Off. Publ. Am. Coll. Allergy, Asthma, Immunol. 104, 1–10 (2010). quiz 2–41.

27. Suchard, J. R. Recurrent near-syncope with flushing. Acad. Emerg. Med. 4, 718–724 (1997).

28. Schmidt, M., Schmidt, S., Adelborg, K., Sundboll, J., Laugesen, K., Ehrenstein, V. & Sorensen, H. The Danish Healthcare System and Epidemiological Research: from healthcare contacts to database records. Clin. Epidemiol. 11, 563–591 (2019).

29. Schmidt, M., Pedersen, L. & Sorensen, H. T. The Danish Civil Registration System as a tool in epidemiology. J. Epidemiol. 29, 541–549 (2014).

30. Schmidt, M., Schmidt, S. A., Sandegaard, J. L., Ehrenstein, V., Pedersen, L. & Sorensen, H. T. The Danish National Patient Registry: a review of content, data quality, and research potential. Eur. J. Epidemiol. 7, 449–490 (2015).

31. Ruwald, M. H., Hansen, M. L., Lamberts, M., Kristensen, S. L., Wissenberg, M., Olsen, A. M. et al. Accuracy of the ICD-10 discharge diagnosis for syncope. Europace 15, 595–600 (2013).

32. Gjerstorff, M. L. The Danish Cancer Registry. Scand. J. public health 39(7 Suppl), 42–45 (2011).

33. Storm, H. H., Michelsen, E. V., Clemmensen, I. H. & Pihl, J. The Danish Cancer Registry-history, content, quality and use. Dan. Med. Bull. 44, 535–539 (1997).

34. Sundhedsdatastyrelsen. Nye Krafte til Fabler i Danmark i 2016. Cancerregisteret. (2017). https://sundhedsdatastyrelsen.dk/da/tal-og-analysen/analysen-og-rapporten/ sygdomme/kraeft_-_cancerregisteret. (2017).

35. Greenland, S. R. K., Lash, T. L. in Modern Epidemiology. 3rd edn. p. 55–56 (eds. Rothman K. J., Greenland S., Lash T. L.) (Lippincott Williams & Wilkins, Philadelphia, 2008).

36. Satagopan, J. M., Ben-Porat, L., Berwick, M., Robson, M., Kutler, D. & Auerbach, A. D. A note on competing risks in survival data analysis. Br. J. Cancer 91, 1229–1235 (2004).

37. Breslow, N. E. & Day, N. E. Statistical methods in cancer research. Volume II-The design and analysis of cohort studies. IARC Sci. Publ. 82, 65–71 (1987).

38. Venkatraman, V., Lee, L. & Nagarajan, D. V. Lymphoma and malignant vasovagal syndrome. Br. J. Haematol. 130, 323 (2005).

39. Ballantyne, F., 3rd, VanderArk, C. R. & Hillick, M. Carotid sinus syncope and cerebral lymphoma. Wis. Med. J. 74, 91–92 (1975).

40. Dubrava, J., Drgona, L. & Kadlecik, R. An unusual cause of recurrent syncope: Mediastinal lymphoma diagnosed with transesophageal echocardiography. Eur. J. Intern. Med. 16, 204–206 (2005).

41. Lichtman, M. A. & Rowe, J. M. Hyperleukocytic leukemias: rheological, clinical, and therapeutic considerations. Blood 60, 279–283 (1982).

42. Oppenheimer, S. The anatomy and physiology of cortical mechanisms of cardiac control. Stroke 24(12 Suppl), 13–15 (1993).

43. Parvisi, J. & Damasio, A. Consciousness and the brainstem. Cognition 79, 135–160 (2001).

44. Christensen, T. D., Spindler, K. L., Palshof, J. A. & Nielsen, D. L. Systematic review: brain metastases from colorectal cancer-Incidence and patient characteristics. BMC Cancer 16, 260 (2016).

45. Rihimaki, M., Hemminki, A., Sundquist, J. & Hemminki, K. Patterns of metastasis in colon and rectal cancer. Scand. J. Gastroenterol. 260 (2016).

46. Badreddy M. B. K. Chronic anemia StatPearls(Internet). (2019). https://www.ncbi.nlm.nih.gov/books/NBK534803/.

47. Burtis, F., Marchi, G., Ugolini, S., Castagna, A. & Girelli, D. Anemia and iron deficiency in cancer patients: role of iron replacement therapy. Pharmaceuticals (Basel) 11, 1–18 (2018).

48. Schiavone, A., Biasi, M. T., Buonomo, C., Nozzoli, C., Roca, M. E., Sambati, R. et al. Micturition syncope. Funct. Neurol. 30, 305–308 (1991).

49. Walker, H. K. in Clinical Methods: The History, Physical, and Laboratory Examinations (eds. Walker H. K., Hall W. D., Hurst J. W.) Chapter 12 (Boston, 1990). .

50. Abdol Razak, N. B., Jones, G., Bhandari, M., Berndt, M. C., Metharam, P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. Cancers (Basel) 10, 1–21 (2018).

51. Sorensen, H. T., Mellemkjær, L., Steffensen, F. H., Olsen, J. H. & Nielsen, G. L. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N. Engl. J. Med. 338, 1169–1173 (1998).

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