



Why wine might be less harmful than beer and spirits

Alcoholic drinks are well known to have carcinogenic properties, and several possible mechanisms have been postulated to explain this. In general terms ethyl alcohol slows down protein synthesis. One obvious consequence of this is that cell repair mechanisms will be inhibited, which could lead to malignant changes. A synergy between alcohol and smoking is also well documented: heavy smokers who also drink heavily are many times more likely to develop oesophageal cancer than non-smokers who drink. In this case the harmful cellular effects of the chemicals and free radicals that are present in cigarette smoke are potentiated if the cells have already been damaged by chronic exposure to alcohol. But perhaps a more interesting question is why beer and spirits are strongly associated with upper digestive tract malignancies, whereas wine is apparently not. One hypothesis involves the action of nitrosamines. These are substances that are found in most alcoholic drinks and which become carcinogenic when metabolised. Among alcoholic drinks, beer usually contains the highest concentrations of nitrosamines (although the concentrations have declined in recent years as a result of changes in malting); distilled spirits also contain them, but at a lower concentration than beers. Typically, wines contain insignificant concentra-

tions of nitrosamines. Animal studies have shown that the presence of ethyl alcohol blocks the metabolism of nitrosamine in the liver (usually mediated by cytochrome *P*-450). As a consequence, the nitrosamines are left intact and free to circulate to other organs, such as the kidneys and oesophagus, where they can be activated into carcinogens. A second line of research supports this theory. Scientists have looked at people who do not have cancer but who live in places with a high prevalence of oesophageal cancer associated with alcohol consumption—such as China and northern France. These people have been found to have a pattern of DNA damage in their oesophageal cells that is closely similar to that known to be caused by exposure to nitrosamines. In addition, the types and sites of mutation of the p53 gene (the tumour suppressor gene) that are commonly found within oesophageal cancer cells also reflect the pattern of DNA damage inflicted by nitrosamines. This confirms nitrosamine-like exposure in cases of oesophageal cancer and could explain why beer and spirits cause more cases of upper digestive tract malignancy than wine.

Abi Berger *Science editor, BMJ*

Population based case-control study of sick leave in postmenopausal women before diagnosis of hyperparathyroidism

Ewa Lundgren, Eva Szabo, Sverker Ljunghall, Reinhold Bergström, Lars Holmberg, Jonas Rastad

Department of Surgery, Uppsala University, S-751 85 Uppsala, Sweden
Ewa Lundgren, consultant surgeon
Eva Szabo, medical student
Lars Holmberg, associate professor
Jonas Rastad, associate professor

Department of Internal Medicine, Uppsala University Sverker Ljunghall, professor

Department of Statistics, Uppsala University Reinhold Bergström, professor

Correspondence to: Dr Lundgren ewa.lundgren@kirurgi.uu.se

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Abstract

Objective: To analyse sick leave in women at risk of primary hyperparathyroidism before its diagnosis.

Design: Case-control study nested within a screened cohort of postmenopausal women. Cases were women with hyperparathyroidism without prior knowledge of their disease and no traditional symptoms or complications. Controls were women from the screened population without hyperparathyroidism.

Setting: Population based screening within a Swedish community.

Subject: 48 case-control pairs of women aged 55–70 years.

Main outcome measure: Sick leave during the 5 years before diagnosis.

Results: Total duration of sickness benefits was longer in the cases than controls, and this discrepancy included sick leave on full time or half time and for periods of longer than a week. Cases had an increased risk of sick leave more than half of the investigated time compared with controls (odds ratio 12). Doctors'

certificates showed that the overrepresented sick leave in the cases related mainly to cardiovascular diseases.

Conclusion: Asymptomatic mild primary hyperparathyroidism in postmenopausal women is accompanied by a previously unrecognised morbidity, which has consequences for clinical management of the disorder and its impact on the health economy.

Introduction

Postmenopausal women are at risk of primary hyperparathyroidism, and many seem to have only mild or no symptoms of the disorder.^{1–3} On the basis of assumptions of a generally benign disease course, surveillance has been advocated in asymptomatic women with uncomplicated hypercalcaemia of a mild to moderate extent.⁴ Detailed evaluation of such patients has shown that they have uncharacteristic symptoms of tiredness and other psychological symptoms, which can improve after parathyroid surgery.^{5, 6} Analyses of the outcome of conservative follow up and surgery may be distorted by patients' knowledge of the existence of a treatable disorder. We carried out a

nested case-control study to examine sick leave before diagnosis and knowledge of mild primary hyperparathyroidism in postmenopausal women recruited by population based screening.

Subjects and methods

Primary hyperparathyroidism was diagnosed in 109 (2.1%) of 5202 women aged 55-75 years attending population based mammography screening.² Diagnosis of primary hyperparathyroidism was based on repeated fasting serum calcium and intact serum parathyroid hormone concentrations and included women with normal serum calcium values.² The disorder was verified histologically in 60 women who underwent parathyroidectomy. For each woman with primary hyperparathyroidism we randomly selected a control matched for age and season of biochemical investigation from the screened population (table 1). Eligibility criteria for cases and controls included a serum creatinine concentration below 160 $\mu\text{mol/l}$ to exclude the existence of severe renal diseases. All women gave informed consent for participation in the study, which was approved by the ethics committee.

All data on sick leave were provided by the regional social insurance office, which recorded sick leave and retirement within the screened population. In 48 (44%) case-control pairs neither the case nor the control had retired, because of age (mandatory retirement age 65 years) or illness, 5 years before the date of screening for primary hyperparathyroidism. The duration, cause, and type of sick leave for these case-control pairs was investigated in the 5 years before the day of screening. This period of time was the length of follow up within the study. Interview at biochemical diagnosis supported the absence of traditional symptoms of primary hyperparathyroidism,⁶ although three cases admitted to constantly feeling tired on direct questioning. Before screening the diagnosis was unknown to all affected women, although two of them had had hypercalcaemia.

Three cases and the same number of controls were housewives at the time of screening. The case or control of 27 pairs had retired because of disease (9 cases, 5 controls) or age (3 cases, 10 controls) during the 5 year period. Both the case and control were excluded from analysis from the date of any full time retirement in the pair to ensure equal years at risk for sick leave. Partial retirement (6 cases, 2 controls) was disregarded. Women with hyperparathyroidism who retired during the study had similar serum calcium and parathyroid hormone concentrations to those who completed the 5 year analysis. The total duration of follow up comprised 348 person years with an individual mean of 3.6 (SD 1.6) years.

For each woman total duration of sick leave was divided by the length of follow up within the study to standardise for variability among the case-control pairs. Benefits on full (100%) or half (50%) time and short (≤ 1 week) or long (> 1 week) time were available during the analysed time period. As these subtypes are partially exclusive recorded days for a particular sickness benefit were divided by the number of days at risk for this particular benefit type. A physician's certificate for sick leave was required only for periods exceeding a week. The diagnoses on the certificates

were grouped according to ICD-9 (international classification of diseases, ninth revision) and could be retrieved for 93% of the periods of long term sickness benefit.

Analysis

We used the Wilcoxon non-parametric tests (Wilcoxon rank sum test and Wilcoxon signed rank test). The relation between the proportion of sick days and case or control status was also analysed on the basis of the logistic regression model estimated by the conditional maximum likelihood method. The variable sick day proportion was calculated as days of sick leave divided by the number of available days. It was considered both in continuous and categorised forms. The exact categorisation was found to be important. $P < 0.05$ was considered significant. Descriptive results are presented as means (SD).

Results

The duration of sick leave differed significantly between the cases and controls (table 2). It was longer in the cases for all benefit types except for those for short term sick leave. Long term sick leave in the cases was greatest for musculoskeletal and cardiovascular diseases and differed from the controls only for the cardiovascular diseases (table 3). The periods of sick leave on full time sickness benefit (mean 164 (SD 348) days *v* 26 (66) days) and long term benefit (220 (387) days *v* 71 (112) days) were longer in the cases than in the controls ($P = 0.010$ and 0.046), but the frequency of periods of sick leave did not differ. The total duration of sickness benefit for cases was not correlated with age or serum calcium and parathyroid hormone concentrations ($r = 0.0006, 0.002, \text{ and } 0.049$, respectively).

The proportion of women who had taken no long term sick leave was similar in cases and controls (27% *v* 25%), but such sickness benefit during half or more of the available days was substantially more common in the cases (27% *v* 2%; table 4). Estimation with the conditional maximum likelihood method of the relation between the proportion of sick days and case or control status confirmed these results. The odds ratio for having a sick day proportion of at least 0.50 was 11.9 (95% confidence interval 1.4 to 105.0) for cases compared with the controls.

Table 1 Clinical characteristics of all women with hyperparathyroidism recruited by screening and of sample of women who had not retired from work 5 years before date of screening. Figures are means (SD)

Variable	All patients (n=109)	Current sample	
		Cases (n=48)	Controls (n=48)
Age (years)	66.6 (5.8)	62.9 (4.1)*	62.7 (4.2)
Serum calcium (mmol/l)†	2.59 (0.14)	2.59 (0.16)‡	2.34 (0.08)
Serum parathyroid hormone (ng/l)§	66.5 (36.3)	68.9 (41.5)‡	29.3 (8.9)
Serum creatinine ($\mu\text{mol/l}$)¶	84 (16.9)	82 (14.5)	82 (10.5)
Parathyroid weight (mg)**	591 (892)††	631 (899)‡‡	Not done

* $P < 0.0002$ *v* all other patients (Wilcoxon rank sum test).

†Ortocresolphthalein dye binding, corrected for serum albumin, normal range 2.20-2.60 mmol/l.

‡ $P < 0.0001$ *v* controls (Wilcoxon signed rank test).

§Allegro IRMA (Nichols Institute, San Juan Capistrano, California), normal range 12-55 ng/l, intra-assay and interassay variation at 27 ng/l of 3.4% and 6.1%, respectively.

¶Reference range 64-106 $\mu\text{mol/l}$.

**Total weight of abnormal parathyroid tissue at operation.

††N=61.

‡‡N=33.

Table 2 Mean (SD) proportion of days of sick leave (days of sick leave divided by available days) and mean (SD) number of days of sick leave taken by women with hyperparathyroidism and by controls

Sick leave	Cases (n=48)		Controls (n=48)		P value*	
	Proportion of sick leave	Days of sick leave	Proportion of sick leave	Days of sick leave	Proportion of sick leave	Days of sick leave
Full time (100%)	0.23 (0.33)	255 (385)	0.08 (0.16)	113 (187)	0.023	0.037
Half time (50%)	0.08 (0.20)	62 (183)	0.1 (0.035)	11 (52)	0.030	0.028
Long term (>7 days)	0.24 (0.35)	309 (477)	0.08 (0.16)	111 (197)	0.008	0.005
Short term (≤7 days)	0.006 (0.007)	8 (10)	0.011 (0.013)	13 (16)	0.021	0.052
Total	0.25 (0.35)	317 (475)	0.09 (0.16)	124 (202)	0.010	0.010

*Wilcoxon signed rank test comparing cases and controls.

Table 3 Mean (SD) days of long term sick leave according to diagnosis in women with hyperparathyroidism and in controls

Disease group (ICD-9)*	Cases (n=48)	Controls (n=48)	P value†
Infectious	3.2 (6.8)	4.4 (10)	0.931
Mental	14 (86)	31 (122)	0.441
Circulatory	111 (345)	1.0 (5.4)	0.017
Respiratory	1.2 (4.3)	13 (54)	0.136
Gastrointestinal	3.4 (11)	2.1 (6.1)	0.398
Musculoskeletal	169 (387)	51 (148)	0.162

*Tumours or endocrine, neurological, and urogenital diseases were rarely or never given as reasons for sick leave.

†Wilcoxon signed rank test.

Table 4 Relation between proportion of sick leave and case-control status with conditional logistic regression. Odds ratios (95% confidence interval) based on 48 women with hyperparathyroidism and 48 controls

Proportion of sick days*	No of cases	No of controls	Odds ratio (95% CI)
0	13	12	1.0
0.01-0.02	7	12	0.5 (0.2 to 1.8)
0.03-0.49	15	23	0.6 (0.2 to 1.7)
0.50-1.00	13	1	11.9 (1.4 to 105)

*Recorded days of sick leave divided by available days.

Discussion

Screening for hyperparathyroidism

Screening for primary hyperparathyroidism was performed mainly to analyse prevalence and symptoms of the disorder in a group of women at risk.² It was attached to population based mammography screening, which is offered every second year to women in Uppsala aged 55-75 years.⁷ The mammography screening was attended by 71% of those invited, which is consistent with findings in other Swedish urban areas.⁸ Since 90% of the women underwent determination of serum calcium concentrations during the investigated 17 month period, 45% of the underlying population was included in the examination for hyperparathyroidism. The recruitment was similar in all age groups.² Only 56% of the women with hyperparathyroidism underwent parathyroid surgery; the remaining women did not have the operation because of personal preferences, severe comorbidity, and mild hypercalcaemia. The patients who underwent the operation had a similar mean age and serum calcium concentrations to those who did not have the operation, which supports the diagnosis in all those recruited by the screening.²

The currently examined cases were representative of all the recruited patients with respect to the serum calcium and serum parathyroid hormone concentrations. Their younger age was expected as women who had retired from work 5 years before the screening were excluded. As the cases and controls were drawn from the same population based screening any selection bias should be minimised. Moreover, recall bias seems unlikely as insurance data were used and the cases were unaware of their hyperparathyroidism before screening. Almost twice the number of cases than of controls retired because of ill health during the investigation, and there was no association between these retirements and serum calcium concentration. The annual duration of sick leave in women with hyperparathyroidism was fairly constant during the 5 year period (not shown), which supports a limited association between the need of sick leave and subsequent retirement. The recorded type and duration of sick leave and the differences in these respects between the cases and controls consequently could reflect true and hitherto unrecognised effects of primary hyperparathyroidism.

Sick leave in undiagnosed hyperparathyroidism

On average the cases were on sick leave for 17% of the investigated time, while the corresponding 7% in the controls approached the value of all postmenopausal Swedish women.⁹ The distribution of sick leave in the cases and controls was skewed. The proportion of cases with at least half of the study period on sick leave was substantially higher than in the controls (27% *v* 2%), and a 12 times higher odds for such sick leave was found. The increased need for sick leave among the women with hyperparathyroidism encompassed all benefit types except for short term leave lasting up to a week. Consistent with the present data, short term sick leave relates mainly to intercurrent infections.¹⁰

Diagnoses on doctors' certificates of long term sick leave are reliable when they are gathered into major disease groups.¹¹ In women with hyperparathyroidism in this study, cardiovascular disorders were overrepresented and musculoskeletal diseases were the main cause of such sick leave. Moreover, no such woman had any period of sick leave due to the specified diagnosis of hyperparathyroidism. Cardiovascular risk factors such as hypertension, hyperlipidaemia, and glucose intolerance, as well as musculoskeletal complications, are recognised phenomena in primary hyperparathyroidism, although the response of some of these disorders to parathyroid surgery is controversial.¹²⁻¹⁴ In some studies of primary hyperparathyroidism, cardiovascular disorders have been proposed as causes of premature death, particularly in older age groups, with complete normalisation after parathyroid surgery.¹⁵⁻¹⁸

Clinical perspective on sick leave in hyperparathyroidism

Primary hyperparathyroidism characteristically is a slowly progressive disease.^{1,5} In our subjects with this condition it was probably present during the entire observation period. Repeated biochemical testing in the 2 years after diagnosis substantiated stable serum calcium and parathyroid hormone concentrations.² Moreover, over a quarter of the women consistently had normal calcium concentrations, and all of them

Key messages

- Primary hyperparathyroidism mainly affects postmenopausal women, many of whom lack classic symptoms and complications of the disorder and are currently considered suitable for conservative follow up
- Postmenopausal women with asymptomatic primary hyperparathyroidism drew more sickness benefit than matched controls during the 5 years before the diagnosis
- Cardiovascular diseases were the main cause of sick leave
- The duration of sick leave was not correlated with age or serum calcium concentration
- Mild undiagnosed hyperparathyroidism in postmenopausal women is linked with previously unrecognised ill health of importance to the clinical and economic impact of the disorder

would have remained undetected without the strict criteria for identification of the disorder that we used.² Parathyroid surgery involved an attempt to explore influences of active treatment under novel circumstances. Currently prevailing criteria with regards to age, serum calcium concentration, and the lack of classic symptoms and complications of hyperparathyroidism would favour conservative follow up in the present cases.⁴⁻⁶ The hitherto unrecognised influences of hyperparathyroidism on sick leave give a new understanding to the morbidity and economic impact of this common endocrine disorder of postmenopausal women. Any influences on the clinical management of this risk group, however, await studies on reversibility of the increased need for sick leave after parathyroid surgery.

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Contributors: The screening of hyperparathyroidism at mammography was a multifaceted project carried out by EL, SL, and JR in collaboration. EL, who was the principal investigator in the project, investigated all the recruited women clinically, participated in their operations, handled all the crude data, and contributed to writing this paper. ES was involved in acquiring and computerisation of data from the insurance office, in the statistical calculations, and in presenting data. SL and JR initiated the idea of screening for hyperparathyroidism at mammography. SL was also involved in practicalities regarding the multitude of studies concerning this screening, the structuring

of data for presentation, and the written presentation. JR generated the study on sick leave and was also involved in all aspects of data interpretation and presentation. RB was the principal statistical expert of the screening project and participated in the planning of the screening examination. LH was involved with statistical analysis and in interpreting and prioritising the data and writing the manuscript.

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Fifty years ago

World Health Organisation

The conception of WHO is one that should appeal to the imagination, and indeed it will call for imagination on the part of those directing its activities if its work is not to be hampered by the natural defence mechanisms of bureaucracy. In full recognition of the great progress already made we may suggest that one of the problems of WHO will be to keep its organization flexible and of such a size that the Director-General will be able to remain in close touch with his staff. In a recent broadcast Sir Lawrence Bragg observed that when an institution grew beyond a

certain size its director—he was of course referring especially to research—lost that close touch with his subordinates which made for efficient and productive team work. Establishments have a natural tendency to grow, but it is to be hoped that the number of permanent officials in WHO will be small enough for the Director-General through personal contact with each one to take that close interest in their work which is essential if an institution is to be something a bit more than an efficient organization. (*BMJ* 1948;iii:303)