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ORIGINAL CONTRIBUTION

Iodine prophylaxis—the protective factor against stomach cancer in iodine deficient areas

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Abstract *Background* Poland has one of the highest death rates for stomach cancer in Europe. Moderate iodine deficiency and in consequence high goitre prevalence led to the implementation in 1996 of a very efficient mandatory model of iodine prophylaxis, based on household salt iodisation (30 ± 10mg KI/1 kg of salt). *Aim of the study* The aim of the study was evaluation of incidence rate of stomach cancer and its possible relation to increased iodine consumption in the years 1992–2004. *Methods* Iodine supply and effectiveness of iodine prophylaxis were evaluated on the basis of comparative analysis of goitre prevalence and ioduria in schoolchildren. To allow comparison between time periods with varying population age structures, the incidence rates of stomach cancer were standardized for age, using the "world standard population". The direct standardization method has been applied. For each sex, the time-trend of incidence rates was shown in graphs over the years 1991–2004. *Results* Evident increase in iodine consumption in this period of time was proved by rise in percentage of schoolchildren (6–8 years old) with ioduria above 100 μg/l from 11.4% in 1992–1993 to 52.9.1% in 2003. It was correlated with the decrease in goitre prevalence from 18.8% to 3.2% respectively. The 24-h thyroid uptake of ^{131}I in investigated population fell from 45.5% in 1986 to 26.8% in 1998. In Krakow the standardized incidence ratio of stomach cancer for men decreased from 19.1 per 100,000 to 15.7 per 100,000, and for women from 8.3 per 100,000 to 5.9 per 100,000 in the years 1992–2004. A significant decline of average rate of decrease was observed in men and women (2.3% and 4.0% per year respectively). *Conclusion* Observed association between improved iodine supply and decrease of incidence of stomach cancer could indicate the protective role against stomach cancer of iodine prophylaxis in iodine deficient areas—further studies are necessary.

Key words gastric cancer – iodine deficiency – iodine prophylaxis

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Introduction

Poland has one of the highest death rates for stomach cancer among European countries (IARC)—something that has resulted in a serious public health problem [1]. The reported risk factors for gastric cancer (Table 1) indicate the pathogenetic association between environmental factors and incidence of stomach cancer [2–4]. Therefore, stomach cancer may be included in the group of preventable non-communicable diseases. Recent comparative epidemic studies in different regions of the world have provided new data on the role of iodine deficiency in carcinogenesis of stomach cancer. The "Venturi hypothesis" [4–6] is based on the correlation between iodine deficiency and high stomach cancer mortality rate. Gastric mucosal cells are capable of concentrating iodides, which in gastric mucosa play an important role as electron donors and antioxidants, and therefore may play a protective role against gastric cancer [7]. Similarity of gastric mucosa and thyroid follicular cell is presented in Table 1. Tissue iodine level is lower in stomach cancer tissue compared with surrounding normal tissue [8]. Lower urinary iodine concentration in patients with stomach cancer was reported recently [9].

Table 1 Similarity of gastric mucosa and thyroid follicular cells

EMBRIOLOGY	Common derivation from a primitive gut
MORPHOLOGY	1. Cells polarity 2. Apical microvilli
MOLECULAR LEVEL	1.NIS 2. Peroxidase system: Thyroid (TPO), Gastric (GPO) 3. Iodide pump
FUNCTIONS	Ability to concentrate iodine resulting in: 1. Synthesis of mono and di-iodotyrosines 2. Strong anti-oxidant properties 3. Regulation of: EOF, DMA synthesis and cell proliferation 4. Secretion of mucinous glycoproteins: thyroglobulin or mucin-correspondly
PATHOLOGY	1. Similar antigens and cross-reactiving antibodies. 2. Simultaneous autoaggressive atrophic gastritis and Hashimoto disease. 3. Thyroid-Gastric Syndrome

Table 2 Iodine pathways in the prophylactic system in Poland

Food grade salt	Daily consumption (on average)
Total salt	10.7 g
Hidden salt (49.5%)	5.3 g
Household salt (50.5%)	5.4 g
Iodide content (30 mg KI/kg)	162.0 μg
Loss due to distribution and technology of cooking (40%)	64.8 μg
Effective iodide consumption	97.2 μg
Effective iodine consumption	73.9 μg[a]

[a]63% of dally iodine intake

Iodine supply level in Poland has been improving markedly through the last 10 years due to the implementation of a very effective model of iodine prophylaxis, based on the obligatory iodisation of household salt with 30 ± 10 mg KI/1 kg of salt [10–12]. It creates an opportunity to assess the relation—in the course of 10 years following the introduction, in 1996, of mandatory model of iodine prophylaxis—between stomach cancer and daily iodine intake.

The aims of the study are as follows:

1. Evaluation of incidence rate of stomach cancer in the years 1992–2004.
2. Comparison of the iodine supply after introducing obligatory household salt iodisation with incidence rate of stomach cancer.

Material and methods

This publication presents data on stomach cancer incidence for population in the city of Krakow in the years 1991–2004. The data were collected and analysed by Krakow Cancer Registry located in the Centre of Oncology M. Sklodowska-Curie Memorial Institute in Krakow. All data were subjected to quality control through assessment of completeness and through assessment of validity. All stomach cancer were classified according to the Tenth Revision of the International Classification of Diseases (ICD-10, cancer of the stomach: C16). The risk of getting cancer increases greatly with age. To allow comparison between time periods with varying population age structures, the incidence rates were standardized for age, using "the World standard population". The direct standardization method has been applied [14]. For each sex, the time-trend of incidence rates was shown in graphs over the years 1991–2004.

The data concerning iodine excretion and thyroid volume were obtained from nation-wide epidemiological study preformed prior to and after implementation of obligatory model of iodine prophylaxis in Poland (1997) in years 1992–1993 and 1999–2003 respectively. The same population of more then 2,500 children aged 6–12 years were analyzed in our study. We assessed the main parameters of iodine deficiency—urinary iodine excretion and goitre prevalence, using the same laboratory (Sandell–Kolthoff's catalytic method) [13] and ultrasound methods (ultrasound device equipped with 7.5 MHz linear transducer). We assessed goitre prevalence according to age-matched thyroid volume normal

Table 3 24-h thyroid uptake of 1311 in euthyroid patients in Poland (1966–2004)

Years	24-h thyroid uptake of ^{131}I (x ± SD)
1966	66.2% ± 13.6%
1986	45.5% ± 6.6%
2000	27.3% ± 10.4%
2004	26.8% ± 9.7%

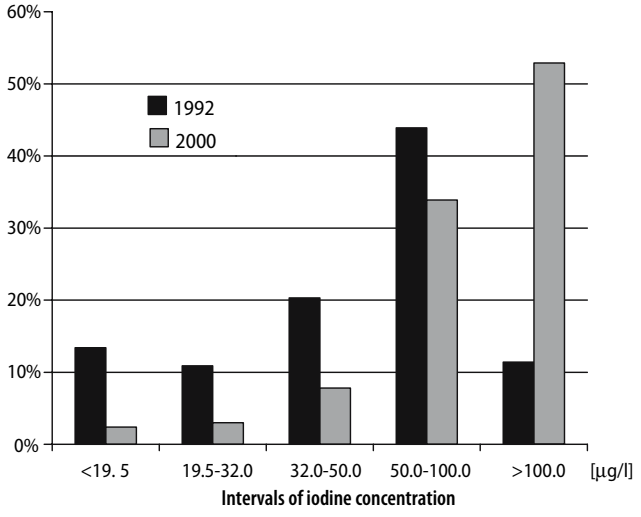

Fig. 1 Urine iodine concentration in schoolchildren (1992 vs. 2000)

values recommended by ICCIDD [15]. Evaluation of iodized household salt production was based on the annual report obtained from the producer—Salt Mine "Klodawa". About 24-h thyroid uptake of ^{131}I was based on the mean values obtained in the years1966–2004 from euthyroid subjects diagnosed in the Department of Endocrinology, Jagiellonian University, Collegium Medicum in Krakow.

Results

Table 2 shows the iodine pathway of iodine intake on the population level, which fulfils a recommended daily iodine intake [16]. Spectacular increase of iodized household salt production from 4,000 tons in 1991 to 135,000 tons in 2004 was noticed. We compared ioduria and thyroid volume in children obtained during nationwide epidemiological survey in 1992–1993 [17] with the data obtained in the years1999–2003.

Figure 1 shows increase of the frequency of iodine concentration in urine over 100 µg/l from 11.4% in 1992–1993 to 52.9% in 2003. Prevalence of goitre in schoolchildren aged 6–8 years decreased on average

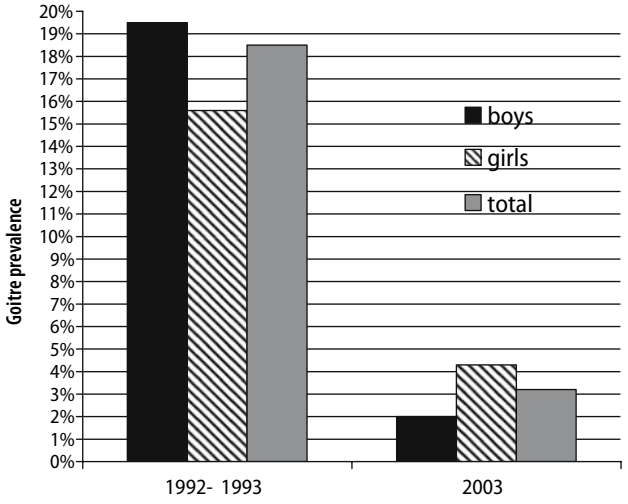

Fig. 2 Goitre prevalence in schoolchildren aged 6–8 years in 1992–1993 and 2003

from 18.5% in 1992–1993 to 5.5% in 2001 and to 3.2% in 2003 (Fig. 2). One of the most sensitive markers of iodine supply on the population level is a reference value of 24-h thyroid uptake of ^{131}I [18]. Table 3 presents decrease of this value from 45.5% in 1986 to 26.8% in 1998. The last evaluation performed by the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and WHO in 2003 [19], transferred Poland to the group of European countries with sufficient iodine supply on the population level.

In the years 1991–1993, the average annual number of new cases of stomach cancer was 81 in men, and 59 in women. The average annual number of new cases from this cancer in 2002–2004 was 82 for men, and 48 for women. In the same time, the standardized incidence ratio for men decreased from 19.1 per 100,000 to 15.7 per 100,000, and for women from 8.3 per 100,000 to 5.9 per 100,000 [15]. The significant decline of average rate of decrease was observed in men (2.3% per year) and also in women (4.0% per year), (Fig. 3, Fig. 4).

Discussion

The hypothesis of causative association between iodine prophylaxis and decrease of incidence rate of stomach cancer is very well founded (Table 2) in the embryologic background and molecular, morphological, functional and pathological similarities of the thyroid follicular and gastric mucosal cells [20, 21]. Gastric mucosal cells have the same sodium/iodide symporter named NIS as thyroid follicular cells, similar hydrogen peroxide peroxidase and are capable

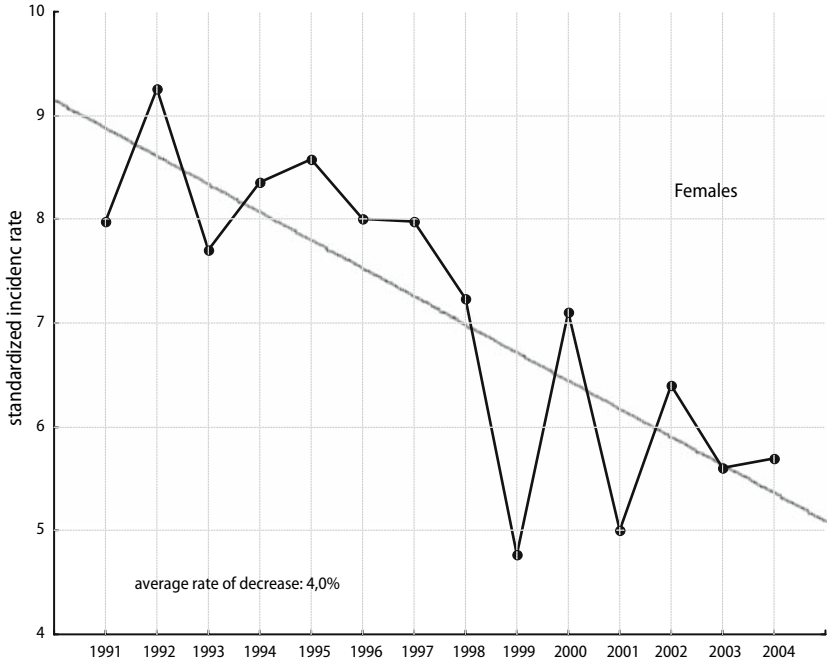

Fig. 3 Incidence rates for stomach cancer in Krakow (1991–2004)—females

of transporting iodine across the mucosal cells membrane creating a negative electric potential (−0.54 V). All these features result in the synthesis of mono- and di-iodotyrosines. Therefore iodine plays an important role as an electron donor, antioxidant, free radicals scavenger, and gastric mucosal cells proliferation regulator. This mechanism can play a protective role against stomach cancer. This approach is supported by an epidemiologic analysis of the stomach cancer mortality rate in the last 10 years in Poland. The overall death rate from stomach cancer in the period from 1991 to 2001 decreased on average by 25% [22]. An association between nutrition factors and stomach cancer was reported in research carried out by Jedrychowski and Popiela in Krakow region who claim that consumption of the Vitamins C and E

Fig. 4 Incidence ratio for stomach cancer in Krakow (1991–2004)—males

carriers (i.e. fruits and vegetables) is inversely correlated with risk of stomach cancer [2, 3] while alcohol consumption and tobacco smoking are the risk factors [23]. These data also correspond with the role of iodine as an antioxidant present in fruit and vegetables. Evaluation of daily intake of the nutrition protecting factors (fruit and vegetables) as well as risk factors (alcohol consumption and tobacco smoking) during last 10 years did not change markedly in Poland [24]. Overall *Helicobacter pylori* infection rate in adult population in Poland increased from 69.9% in 1996–1999 [25] to 78.5% in 2000–2003 [26]. The above mentioned data do not allow one to presume that listed risk factors have changed and that this is the true cause of drop in stomach cancer incidence in Poland.

However, an effective iodine prophylaxis has been developed from 1996 up to the present time. Obligatory model of household salt iodisation (30 ± 10 mg of KI/1 kg of salt) resulted in increase in the concentration of iodine in urine of schoolchildren to recommended average level—100 μg/l, endemic goitre in the youngest groups of children decreased below endemic level (2.7%), and the most sensitive marker on the population level, 24-h thyroid uptake of ^{131}I, decreased from 45.5% to 26.8%. In the comparable period of the time from 1992 to 2004, the age-standardized incidence ratio of stomach cancer in men decreased by 17.8% and 28.9% in women, while long-term observations show constant increase of cancer incidence in both sexes for all cancer sites. In the years 1991–2004 in Krakow, the age-adjusted incidence rate increased from 255.5 per 100,000 to 287.0 per 100,000 in men, and from 194.1 per 100,000 to 251.9 per 100,000 in women [15]. Similar association between iodine deficiency and increased risk of gastric cancer was reported recently (2006) in a Chinese cohort of 29,584 adults by Abnet et al. where association between H. pylori seropositivity and goitre in population was not found [27] and therefore, confounding by *H. pylori* is unlikely to explain the observed association between iodine-deficient goitre and risk of gastric cancer [27]. Kandemir et al. found a higher frequency of goitre in patients with gastric cancer compared with healthy control subjects [26]. A more recent paper, from the National Cancer Institute, reported that *H. pylori* seems to protect against cancer of the upper stomach that includes the junction of the esophagus [29, 30].

Thus, we may assume that the relevant cause of significant decrease of stomach cancer incidence—under the specified conditions in Poland—could be iodine prophylaxis. Recognition of iodine deficiency as one of the risk factors of stomach cancer strongly supports the necessity for implementation of the effective iodine prophylaxis in iodine deficiency areas [31].

Conclusions

1. A close association between improved iodine supply and decrease of incidence rate and death rate for stomach cancer after implementation of the effective iodine prophylaxis in Poland supports the "Venturi hypothesis" and are in agreement with similar observations in different areas of the world.
2. The data obtained point to the possible protective role against stomach cancer of effective iodine prophylaxis in iodine deficient areas.

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