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The Impact of Geographical, Clinical, Dietary and Radiation-induced Features in Epidemiology of Thyroid Cancer

Werner Langsteger, Peter Költringer, Gerhard Wolf, Karin Dominik, Wolfgang Buchinger, Georg Binter, Sigurd Lax and Otto Eber

Cancer of the thyroid accounts for less than 1% of all cancers recognised each year, but the incidence is rising. Much of the early work of the epidemiology and aetiology of thyroid cancer was based on the assumption that thyroid cancer can be treated as an entity. The recognition that two distinct types of endocrine cell occur within the thyroid has made it clear that any discussion of the aetiology and epidemiology of thyroid malignancies must take into account the histological classification of these tumours. Moreover, there are difficult problems to be considered when comparing thyroid cancer incidence across tumour registries, because of a lack of standardisation of morbidity data collection, difficulties in histological diagnosis, varying rates of diagnosis of occult papillary carcinoma, and prevalence and techniques of autopsies. So far only a relatively small proportion of thyroid cancer cases can be explained with adequate certainty as regards epidemiology and aetiology. As in cancer in general, the aetiology and epidemiology of thyroid cancer in detail remains unknown in the majority of cases.
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INTRODUCTION

EPIDEMIOLOGY OF thyroid cancer contains mostly findings and data concerning frequency and can help to define the cause and pathogenesis as well as therapy and prevention of thyroid carcinomas. With an incidence of 1–3/100 000 and a frequency of < 1% out of the total rate of malignant tumours in the population, clinically relevant thyroid malignancies are equally rare in almost all countries [1].

The distinction between factors that act as initiators of thyroid cancer and those that act as promoters may be of clinical importance. Factors that stimulate the thyroid may not be sufficient to cause thyroid cancer but may promote it. The three most important factors and agents—alone or in combination—which can cause or contribute to thyroid carcinomas are (1) geographical features, (2) patient features and (3) radiation.

1. GEOGRAPHICAL FEATURES

Endemic goiter

There are important geographical variations in the frequency of papillary, follicular and anaplastic thyroid cancers. In countries where endemic goiter is common, more follicular and anaplastic carcinomas are typically found. Attempts to compare the frequency of thyroid cancer in geographical areas with and without endemic goiter have given discordant results.

Switzerland. In 1924 iodised salt prophylaxis with 5 mg KJ/kg was introduced; in 1930 the dose was increased to 10 mg. In 1928 Wegelin [2] reported that from 1917 to 1927, 6.9% thyroid carcinomas were detected in 2823 goiter operations in Bern; this was 10 times higher than in goiter-free Berlin. From 1940 to 1950, 5.4% thyroid malignancies were detected in 7457 goiter operations [3]; histologically, there were 11% papillary, 33% follicular and 25% undifferentiated carcinomas.

Nevertheless, the higher iodine dose in iodine prophylaxis has resulted in a shift from undifferentiated to highly differentiated (especially papillary) carcinoma and thus also a shift in ratio from follicular to papillary carcinomas [4]: from 1967 to 1977 31% papillary, 42% follicular and 12% anaplastic thyroid carcinomas were histologically diagnosed in Bern [5]. This change in tumour spectrum has also been accompanied by a reduction in mortality rate.

As 20% of individuals under the age of 40 had goiter identified by clinical examination, and in 30% of the Swiss population the urinary excretion of iodine indicated iodine deficiency [6, 7], the iodine content of table salt, therefore, has been increased finally from 10 to 20 mg KJ/kg in 1980.

Austria. Results similar to those in Switzerland—both countries can be regarded as classic alpine endemic regions—were also found by Hofstätter in Austria, in the Tyrol [8] when comparing the data for frequency and morphology of thyroid carcinoma before and after the introduction of iodine prophylaxis.

According to the most recent studies from 1985 to 1987, 280 new cases of thyroid cancer were registered annually in absolute figures, and 3.5/100 000 in relative terms, respectively (Table 1). The provinces of Upper Austria, Salzburg, the Tyrol and

Table 1.

	$T_{0-2}N_0M_0$	$T_{0-2}N_{1,2}M_0$	$T_{3,4}N_3M_1$
Austria 1972	19.2%	9.8%	71.0%
Austria 1978	34.8%	4.8%	60.4%
Austria 1983	67.5%	5.6%	26.9%

Correspondence to W. Langsteger.
W. Langsteger, P. Költringer, K. Dominik, W. Buchinger, G. Binter and O. Eber are at the Department of Internal Medicine and Nuclear Medicine, Barmherzige Brüder Graz-Eggenberg, Bergstrasse 27, A-8021 Graz; G. Wolf is at the 1st Department of Surgery; and S. Lax is at the Pathological Department, University of Graz, Austria.
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Vorarlberg [9] had figures above the Austrian average, whereas Styria, as a case of extensive iodine supplementation, only showed the Austrian average frequency of thyroid carcinoma [10]. Furthermore—as in Switzerland—the almost identical histological spectrum leads to an increase of fortuitously detected papillary microcarcinomas [11].

United States of America. In 1924 goiter prophylaxis was introduced with 100 mg KJ/kg salt; the goiter prevalence in school children in Michigan was reduced from an average of 38.6% in 1924 to an average of 1.4% in 1951 [12, 13].

Similar to the above data from Switzerland, papillary carcinoma was found in 30% between 1907 and 1937 and in 61.3% between 1938 and 1947 [14].

Columbia. In 1955 Gaitan [15] observed an 85% goiter prevalence in the whole population of the Cauca Valley; from 1956 to 1963, the incidence of thyroid carcinoma in this valley was 6.3/100 000 in males (cf. 0.95/100 000 in New York).

Despite adequate goiter prophylaxis, in the period from 1959 to 1974 goiter prevalence in children in the same valley was in the range of 1 to 42%. Up to now the highest known incidence of follicular and anaplastic thyroid carcinoma exists in some areas of severe endemic goiter in Columbia; the possible explanation are disulfides of saturated and unsaturated aliphatic hydrocarbons in drinking water coming from sedimentary rocks.

Japan. In comparison with western countries and endemic goiter areas the iodine intake and, therefore, the frequency of papillary carcinoma in Japan is believed to be higher, and that of undifferentiated carcinoma low [16–18]. Only 0.8% of all malignant tumour cases in the period from 1966 to 1977 were cases of thyroid carcinoma. In 1979 the incidence of thyroid cancer in Japan was 2.92/100 000 in females and 0.77/100 000 in males [19].

Dietary iodine

Among the potential factors that may account for thyroid cancer, dietary iodine appears to be especially important. In the past three decades, a number of studies have shown that iodine supplementation added to a population's diet causes the prevalence of papillary thyroid carcinoma to rise, whereas the prevalence of follicular and anaplastic thyroid cancers declines.

Excessive iodine intake. Studies of the effects of iodine supplementation have yielded inconsistent results. In 1971 Doniach [20] reported that in Iceland and Hawaii—both areas with a high iodine intake—the incidence of thyroid carcinoma was 6/100 000, as compared to an incidence of 1.5/100 000 in Denmark and England with an average iodine intake.

The evaluation of Caucasians, Chinese and Japanese in their ethnic homeland and in Hawaii indicate a higher rate of thyroid carcinoma in Hawaii; therefore, geographical differences suggest environmental rather than genetic influences [21]. Nevertheless genetic influences may also be important because the incidence of thyroid carcinoma in Hawaii is three to four times higher in the Chinese population (16.9/100 000) than in Japanese and Caucasian populations [22, 23]. This high risk for all ethnic groups in Hawaii suggests the importance of a local environmental aetiological aspect. Both in Hawaii and in Iceland the carcinogenic agent is possibly contained in volcanic lava [24]. The high iodine consumption in Iceland came from iodine-rich sea fish and milk, since dairy cattle are fed large amounts of fish flour; milk contains four times more iodine than in Scotland. During a 20-year period 108 malignant thyroid tumours were processed: the relative incidence of papillary carcinoma was 71% in Iceland and 54% in Scotland, the follicular carcinoma incidence was relatively lower in Iceland (11%) than in Scotland (15%). Therefore, the authors assumed that the incidence of papillary and follicular carcinoma is influenced separately by dietary iodine, because of the direct correlation between high iodine intake and the incidence of papillary carcinoma, in contrast to the direct correlation between iodine deficiency and the incidence of follicular carcinoma. On the other hand, undifferentiated carcinoma was two times more frequent in Scotland than in Iceland (in 26% of surgical material).

Iodine deficiency. Environmental factors, such as iodine deficiency, are thought to operate through the action of thyrotropin (TSH). There is considerable evidence in animal experiments that prolonged TSH stimulation can cause and promote thyroid neoplasms. The evidence in humans is equivocal [25].

Nodular goiters have a stronger tendency towards malignant degeneration [26]; the rate of carcinomas after radiotherapy is higher when an iodine deficiency diet [27] or goitrogenic substances [28] have been administered simultaneously. It is safe to assume that iodine deficiency alone has no influence on the rate but merely on the histological type of thyroid carcinomas. Rolon [29] pointed out that the change in the histological distribution of the thyroid carcinomas, the increase of papillary and the reduction of follicular carcinomas produced by iodisation allows us to conclude that papillary carcinoma is the 'original' carcinoma in the thyroid gland and that the follicular carcinoma may be an evolutionary stage originating from iodine insufficiency.

Another point to be mentioned is that an association of HLA-DR1 antigen with differentiated thyroid carcinoma was found in Italy and Hungary [30, 31], and of HLA-DR7 in the American mid-west [32]; these positive findings are in contrast to an examination in Newfoundland, where no HLA association was observed [33]. As southern Italy and eastern Hungary are iodine-deficient areas, it could be possible that iodine deficiency predisposes HLA-DR1-positive individuals to thyroid cell transformation.

TSH as a 'promoting factor' can be considered a common link between benign hyperplasia and carcinogenesis; it also influences tumour formation based on various mutative or initiating factors, e.g. chronical iodine deficiency, goiterogenic substances such as thiouracil [34]. In the last decade, however, the role of TSH as a direct growth stimulater has been called into question [35].

Long-term stimulation promotes, via hyperplastic intermediate stages, tumour formation. A chemical carcinogen plus TSH stimulation will increase the incidence and shorten the latency period of thyroid cancer. Early hypophysectomy reduces the occurrence of carcinomas, as has been proved by animal experiments [36, 37].

Discrepancies exist on the correlation between malign struma and long-term TSH stimulation: Heinze found a positive correlation based on 20–30% carcinoma patients after strumectomy [38]. Halter, on the other hand, discovered thyroid malignancies in only 7.5% of the patients who had undergone strumectomy so that he considered a causality between struma recurrence and the occurrence of thyroid carcinoma to be rather unlikely [39].

2. PATIENT FEATURES

Many studies have considered the possibility that thyroid cancer is preceded by other thyroid abnormalities, including

benign thyroid nodules, lymphocytic thyroiditis and Graves' disease. Because these thyroid diseases are common, it is important to know whether patients with them should be considered at increased risk of developing thyroid cancer. Despite considerable efforts to resolve this question, the findings remain somewhat conflicting and, therefore, inconclusive.

Graves' disease

Intensive hyperplasia with a rapid enlargement of the thyroid gland are characteristic of Graves' disease. There is increasing evidence that Graves' disease influences the development of thyroid carcinoma and the tumour's subsequent behaviour. Thyroid carcinoma occurs in 5 to 10% of patients with Graves' disease treated with thyroidectomy [40]. Belfiore and colleagues [41] recently reported a 46% incidence of thyroid carcinoma in Graves' disease patients with palpable nodules. In this important study, tumours in patients with Graves' disease were substantially larger and displayed more aggressive behaviour than those in other patients.

In a larger series of 576 patients with papillary carcinoma only 3% of the patients had Graves' disease [42]; Wahl *et al.* also mentioned hyperthyroidism in 4.2% of 544 patients operated on for thyroid cancer [43].

In 1966 Olen and Klinck [13] recorded 2.5% mostly occult carcinomas in 2114 of surgical specimens; in 1970 Shapiro [44] found 8.7% unsuspected carcinomas in a consecutive series of 172 thyroidectomies in patient with Graves' disease. In 1971 3.8% papillary carcinomas in 500 patients were observed in a Greek population; the female : male ratio was 5:1 [45].

Nevertheless, thyroid cancer may be associated with hyperthyroidism in various ways. The incidence of thyroid carcinomas in patients treated for hyperthyroidism from 1946 to 1968 in 25 medical centres in the U.S.A. and England was 2.5% [46]. The patients were treated with 131[I], surgical thyroidectomy, antithyroid drugs, X-ray irradiation and various combinations of therapeutic regimens.

Autoimmune thyroiditis

It is still not known why the incidence of thyroid carcinoma is two to three times higher in women than in men. On the one hand are reproductive functions or the increased propensity to develop euthyroid and hyperthyroid goiter, on the other hand is a higher incidence of Hashimoto's thyroiditis which may account for this phenomenon [47]. 9287 surgical thyroid specimens, collected between 1920 and 1963 at the university hospital of California, were examined; the detailed data of this study [48] showed:

(a) Lymphocytic thyroiditis in abnormal thyroids was found in 8.1%, thyroid carcinoma in 4.7%.
(b) The combination—thyroid carcinoma with lymphocytic thyroiditis—was almost 10 times more common than thyroid carcinoma without thyroiditis (22.5:2.4%).
(c) No significant difference in the frequency of lymphocytic thyroiditis in patients with tumours more or less than 10 mm in diameter.
(d) In 65% of papillary carcinomas and 92% of all tumours lymphocytic thyroiditis was observed inside, outside or both inside and outside of the tumour.
(e) The survival rate was significantly longer in patients with combined papillary carcinoma and lymphocytic thyroiditis than in patients with papillary carcinoma alone.

As regards the last point, Goudie also postulated in 1969 that lymphocytic thyroiditis in and around papillary carcinomas represents a protective process, preventing the formation of metastases in regional lymph nodes [49].

Genetic abnormalities

Evidence suggests that there are factors, probably genetic in nature, related to the possibility of developing radiation-induced thyroid neoplasms. Patients with one radiation-induced tumour (thyroid, salivary or benign neural) are more likely to develop another tumour than patients exposed to the same amount of radiation and with comparable risk factors [50, 51].

Some medullary and papillary carcinomas also belong to this category. Papillary carcinomas can occur with Gardner's syndrome (dominantly inherited familial polyposis of the large intestine and predisposition to the development of colon and rectum carcinoma in early adulthood) [52, 53]; the other is Cowden's disease, autosomal dominantly inherited multiple hamartoma syndrome [54].

Inborn errors of metabolism

In these very rare cases high secretion of TSH was involved in the carcinogenesis of the extremely hyperplastic thyroid tissue; additionally, more cases of thyroid carcinoma as complication of Pendred's syndrome should be expected [55].

Pharmaceutical agents and toxins

Although no pharmaceutical agent or toxin has been proved to cause thyroid cancer in humans, there are reasons to remain open to this possibility. Drugs such as lithium and phenobarbital are known to cause goiter and elevation of serum TSH. These observations make it reasonable to suspect that certain drugs could cause or promote the growth of thyroid cancer. Studies in laboratory animals support the hypothesis that agents that stimulate TSH may cause thyroid cancer [56].

Patients with congenital goiters have thyroids that are subjected to intense stimulation by TSH until they are appropriately treated. Rare patients with congenital goiters who have developed thyroid cancer have been reported, supporting the possibility that intense TSH stimulation alone is sufficient to cause thyroid cancer in humans [57].

Hormonal factors

Thyroid cancer occurs more frequently in women, suggesting that hormonal factors are involved in its pathogenesis. Human studies to further define these factors have not been revealing. One potential exception is the case–control study of thyroid cancer in Connecticut that showed that pregnancy was related to thyroid cancer [58]. The elevated levels of thyroid stimulators during pregnancy is a potential explanation of this observation.

Furthermore, the higher frequency of malignant growth in women may be explained by the finding that in animal experiments the simultaneous administration of oestrogen [59]—during an extended period—produced a significantly higher rate of malignancies in female than in male animals. Testosterone had no such effect.

Also, a steroid imbalance after treatment with prednisone in juvenile rheumatoid arthritis and SLE in the aetiology of thyroid carcinoma could be possible [60].

3. RADIATION

The relationship between radiation and thyroid cancer was first recognised by Duffy and Fitzgerald in 1950 [61]. They found that an unusually large fraction of their patients with

thyroid cancer had a history of radiation therapy. Although these studies were initially doubted, the relationship was confirmed by a wide variety of studies.

In the U.S.A. as many as 80% of children with thyroid carcinoma had a history of previous radiation of head and neck, because they were irradiated for cutaneous haemangioma, keloid, acne vulgaris, tinea capitis, pertussis, enlarged tonsils and adenoids, medulloblastoma, Hodgkin's disease and so-called thymic enlargement. The doses administered were between 0.5 and 5 Gy.

World-wide observations have proved that relatively low antiphlogistic radiation doses are sufficient to induce tumours. The mean time of induction is 8–9 years [62]; the minimum period of induction was 5 years [63, 64]. The development period of the tumour until recognition of the carcinoma may be as long as 20–22 years [37, 65, 66], however, tumours have become manifest even after a period of 40 years.

The majority of thyroid malignancies in childhood were highly differentiated tumours; in 72% the carcinomas were papillary in nature and in 19% they were follicular, usually with a relatively high proportion of oncocytic subtypes [62]. The biological behaviour is relatively favourable: at the time of first histological diagnosis, regional lymph node metastases were present in 74%, they were bilateral in 32% and lung metastases were found in only 14%; the mortality rate was below 20%.

These results were supported by Japanese studies on patients who in 1945 had lived in the area above where the nuclear bomb had been released. This strongly underlines the particular high sensitivity of juvenile thyroids to radiation, and these findings have, moreover, also been sufficiently corroborated by results from animal experiments [67].

Finally, the accident in Chernobyl in April 1986 may lead to an increase of thyroid cancer of 0.1% during a period of 25 years; these data are based on 131[I] and 133[I] uptake measurements [68]. The life time risk for children will probably prove to be greater than for adults because of the prolonged latent period and the child's longer potential lifespan relative to the adult. This was documented by Conard *et al.* in a study on inhabitants of the Marshall Islands, who had been exposed to the thermonuclear bomb testing over the Bikini-Atoll [69, 70].

Only one aspect of natural ionising radiation should be mentioned: a small landstrip in the south western corner of India, named Chavara-Neendakara is known for its high natural radiation level produced by thorium and some uranium in the black monazite sand (average exposure to gamma and beta radiation about 1500 mrad/year). From 1953 to 1966, 1311 surgical thyroid specimens were examined. Thyroid carcinoma was found in 18% and this was 2.5 times higher than in goiter-free New Dehli. At the same time, goiter prevalence was 50% lower than in the corresponding areas ([71], unpublished data from Thangavellu in 1966).

Finally, it appears to be proven that radioiodine therapy does not increase the frequency of carcinomas in adults [46, 72].

COMMENTS

Numerous publications on thyroid carcinomas begin with the listing of epidemiological data; however, the only comprehensive study known to date is apparently the work by Doll *et al.* from 1966 with a register from 25 states [73]. The discrepancies existing in almost all epidemiological studies between the true rate and the number of discovered malignancies may be due to the different statistics of postmortem and operated cases, as well as to the intensity and quality of histological work.

Considerable regional differences in the intensity of diagnostics, the selection of cases, the willingness or reluctance of the surgeon to operate, as well as histological interpretation, play an essential role so caution is advised when trying to draw conclusions as regards regional differences.

When looking at or trying to evaluate geographical aspects, the rates of cancer in different endemic regions cannot be compared with one another epidemiologically [74, 75]. Mortality of thyroid tumours rises almost logarithmically with increasing age [76]. In males we have a steadily increasing incidence with age, whereas for females the incidence rises rapidly in the third decade of life and then stabilises.

Except for some regional exceptions, the tumour distribution as regards age and sex depends on its histology [77]; (a) follicular carcinomas occur preferably beyond the third decade, females are more likely to be affected than males, (b) papillary carcinomas are present especially in women in their fourth to fifth decades, (c) undifferentiated carcinomas prevail from the sixth decade onward.

In non-endemic regions (Table 2) cold nodules turn out to be carcinomas in up to 25% of the cases; in endemic regions in only 6% of the cases—i.e. a more progressive approach is indicated in non-endemic regions [78]. The incidence of malignancy in multinodular stroma is lower in endemic regions than in solitary cold nodules outside endemic regions and in cold nodules of juveniles.

The occult papillary carcinoma (OPC) with a diameter of < 5 mm has been especially discovered in autopsies with frequencies between 5.6% in Columbia and 35.6% in Japan: multicentricity was found in 46% and regional lymph node metastases in 14% [79]. In operations the frequency varies between 13 and 34% [72]. The biological significance is most probably very low, since local recurrences or metastases have never occurred, not even in sufficiently long follow-up periods [80]. One consequence from this fact is the need to treat this type of tumour as a separate entity when determining therapeutic outcomes; nevertheless, one should bear in mind that tumours as small as 0.5 mm in diameter may be able to metastasise into regional lymph nodes [81]. However, the figures are not exactly comparable because the thyroids have been examined by different methods [26–28, 82]. No definite correlation was found between the incidence of OPC and sex or age [29].

The growth or disappearance of papillary carcinoma in general is affected by various factors, including the proliferative activity and antigeniecity of the cancer cells, the host reactivity and promoting factors [29]. Fukunaga *et al.* suggest that TSH may be a promoting factor in humans, and the fact that its level is

Table 2.

Country	Goiter prevalence (%)	Incidence (%)	Source
Austria	35	3.5	Riccabona 1983
F.R.G.	16.5	~ 10.5	Oberdisse *et al.*, 1980
Greece	~ 20	12.4	Oberdisse *et al.*, 1980
Sudan	~ 35	1.5	Oberdisse *et al.*, 1980 Hetzel and Stanbury, 1980
Switzerland	25	22	Oberdisse *et al.*, 1980
U.K.	< 10	11.4	Oberdisse *et al.*, 1980
U.S.A.	< 10	20.5	Oberdisse *et al.*, 1980

Table 3.

Factor's significance	Characterisation	Responsible for x% of thyroid carcinoma
	Radiation to neck and upper chest	1%
	Chronic TSH stimulation of existing goiter	2%
	Hashimoto's thyroiditis	0.5%
Well-defined	Genetic influences	~ 1%
Possibly important	Viral infections 'oncogenes'	~ 10% (?)
	Other environmental factors?	~ 84.5% (?)
	Iodine excess?	
Unclear	Iodine deficiency?	

higher in females than in males would explain the higher incidence of clinical thyroid carcinomas in female [82].

Discrepant factors, which can neither be explained nor proved, are that in the extremely iodine deficient region of the Himalayas thyroid carcinomas are not very frequent [83]. In the iodine-rich costal region of Norway, on the other hand, carcinomas are more numerous than in the interior of the country [84]. Iceland and Hawaii, countries with the highest incidence of carcinomas, are not regions with iodine deficiency.

Seventeen (6.5%) latent carcinomas in Israel were found in 260 consecutive autopsies of patients over the age of 20; in 2 cases diffuse metastases were present in the lung. The tumours were more frequent in Jews born in Europe, but there were no significant differences between specific countries or regions [85, 86].

A relationship between thyroid carcinoma and psoriasis [85], drinking water sources [87], previous breast cancer [64, 88], obesity among women [17, 64], alcohol [89] and dietary calcium and vitamin D [90] intake is significant in thyroid carcinoma, is questionable, difficult to explain and may just be a chance event.

All these somewhat controversial issues which are raised in this paper permit us to conclude that the aetiology and pathogenesis of thyroid cancer is multifactorial in its nature (Tables 3, 4). However, epidemiological data can rarely be compared directly with one another, so that only the observation of trends provides a better insight and more detailed explanation.

Epidemiological studies of thyroid carcinoma in humans and dogs, as well as experimental thyroid carcinogenesis in rodents, indicate that prevention of endemic and some forms of sporadic goiter, combined with substitutional therapy, can significantly reduce the morbidity and mortality of thyroid carcinoma in humans.

A goiter policy should include regulations and methods for preventing nutritional deficiency and excess of iodine, combined with elimination of antithyroid effects of natural and synthetic goitrogens, avoidable ionising irradiation of the thyroid (which is also a goitrogen), and elimination of other types of adverse factors that may appear in the future. Clinical medicine should offer early and continuous substitutional therapy of all non-toxic goiter and an immediate and permanent full suppressive hormonal postoperative therapy of goiter.

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Table 4.

	Low I diet	High I diet	Radiation	Precursor cancer	Inheritance	Racial predisposition	Thyroiditis
Papillary carcinoma	−	++	++	−	+	+	−
Follicular carcinoma	++	−	+	−	−	−	−
Anaplastic carcinoma	−	−	+	++	−	−	−
Medullary carcinoma	−	−	+	−	++	−	−
Lymphoma	−	−	−	−	−	−	++

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Colon Cancer in Seven Siblings

Parviz Ghadirian, Marcel Cadotte, André Lacroix, Jacques Baillargeon and Chantal Perret

In a case–control study of cancer of the colon it was found that 96 out of 332 (29%) cases had a positive family history of cancer of the colon (2 cases and more) as compared with 19 out of 473 (4%) controls. 3 colon cancer cases reported that 6 of their respective relatives were also affected with the same cancer. We were able to do a complete follow-up study of one family where 7 out of 12 sibling ($P < 0.05$) had confirmed pathological diagnoses of cancer of the colon. The mean age at diagnosis among these familial colon cancer cases was 64 years (60 years for females and 73 years for males) and all tumours were located in the caecum or right colon (a common characteristic of colon cancer in this family). There was no history of familial adenomatous polyposis in this family. It is unlikely that the significantly high proportion of familial colon cancer found could be due to chance. This suggests that both environmental and genetic factors play an important role in the aetiology of colon cancer.
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INTRODUCTION

CANCER OF the large bowel is the second most common cancer both in terms of incidence and mortality for both men and women in most of the developed countries of the world. The highest incidence rates are from the U.S.A., Canada and New Zealand, while the lowest rates have been reported from Asia, Africa and Latin America [1].

The highest rates of colorectal cancer appear among those aged 65 years and over, and male:female ratios of less than unity are more frequently observed for cancer of the colon than for other cancers [2]. Countries with high rates of stomach cancer tend to have low mortality rates from colorectal cancer, and vice versa [3]. People living in rural areas tend to have lower rates of colorectal cancer: a prominent feature of large bowel cancer is that urban populations are at high risk [4–7].

American Indians have a rate less than half that for U.S.A. whites [8]. Mormons in the U.S.A. have lower rates of colorectal cancer than the population as a whole [9, 10]. This is also true