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ENDOMETRIAL ADENOCARCINOMA IN THE MALTESE POPULATION AN EPIDEMIOLOGICAL STUDY

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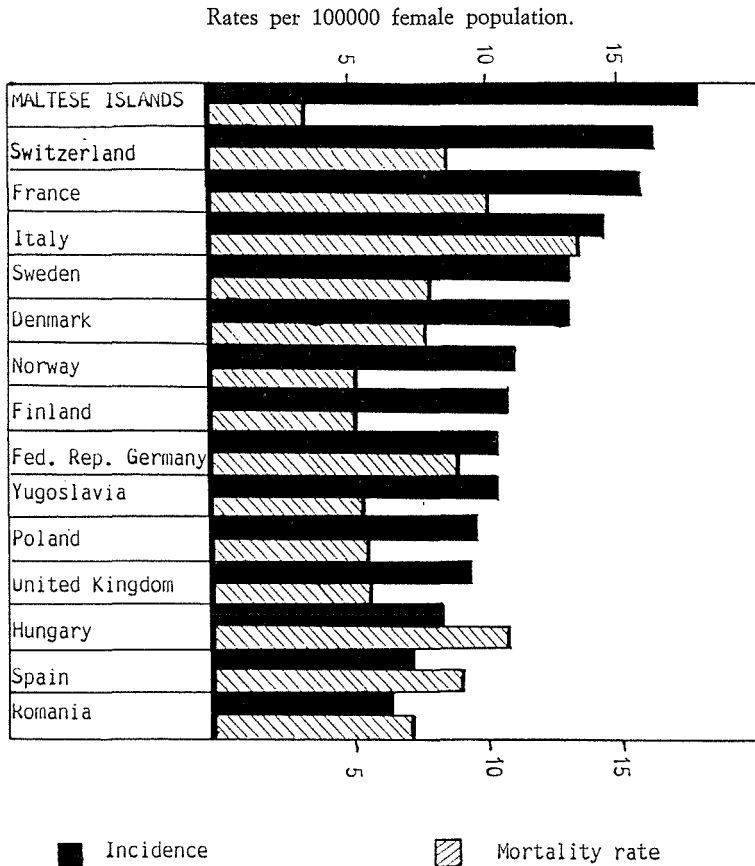
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Summary: The Maltese population has been shown to have a high incidence of endometrial adenocarcinoma when compared to other European countries. This high incidence has been correlated to the high prevalence of abnormal glucose metabolism and rather high dietary fat intake in the Maltese population. Hypertension and low parity were also found to be more frequent in the carcinoma group.

INTRODUCTION

The endometrium is the fourth most common site of invasive carcinoma in women and the most common gynaecological malignancy. Endometrial adenocarcinoma constitutes over 90% of the neoplasms involving the uterine corpus. For many years there had been a relative lack of interest in endometrial cancer by oncologists because of its low virulence and correspondingly low mortality rate relative to other cancers. The realization that this cancer was probably a hormone de-

pendant malignancy revived interest in the epidemiology of the disease. It has now been associated with women who were the subjects of constant oestrogen stimulation without progestational modification. This study attempts to review some epidemiological features of endometrial carcinoma in the Maltese population. This population in 1981 comprised a relatively closed community of 319936 individuals, with a female-male ratio of 1.3, about 23.7% of the female population were aged 50 years or more (3). The Mal-



(References: Waterhouse et al., 1982; Who, 1983)

Fig. 1. — Incidence and mortality rates European Region.

incidence of a malignancy commoner in these population has been found to have a high prevalence of Type II diabetes mellitus and impaired glucose tolerance⁽¹⁶⁾, conditions which have been associated with an increased risk of endometrial cancer.

MATERIAL AND METHODS

The records of all the patients with endometrial adenocarcinoma diagnosed by hystopathology at St. Luke's Hospital, Malta during the 1979-1983 period were reviewed. St. Luke's

Hospital is the main hospital in the Maltese Archipelago accounting for a very large percentage of major operations performed on the Islands. Patients with endometrial adenocarcinoma are very likely to be referred to this hospital. Thus statistic from the hospital may be considered to be representative for the whole Maltese population.

During the period 1979-1983, there were a total of 121 new cases of endometrial adenocarcinoma diagnosed by histo-pathology, giving an overall national incidence of 14.6 per 100,000 female population. Of these cases, 17 were excluded from the epidemiological study because the case records could not be traced, though data regarding the patient's age and locality was available. The National statistics were obtained

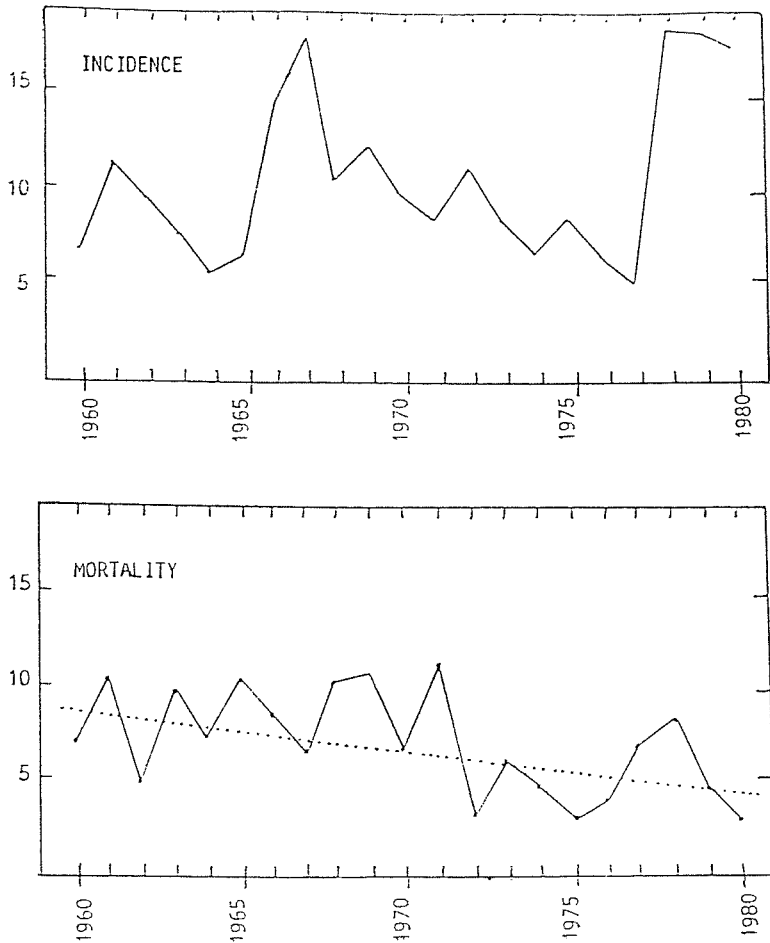


Fig. 2. — Trends in incidence and mortality rates of uterine corpus malignancy in Malta.

from published sources^(3,4) and from the Cancer Notification records of the Department of Health in Malta.

INCIDENCE PATTERNS

The vital statistics of this type of cancer, in terms of international comparisons, are difficult to evaluate since endometrial adenocarcinoma is often recorded together with other malignancies of the corpus uteri. The latter group comprising sarcomas and mesodermal tumours account for only

a small proportion of cases. During the period 1979-1983, these tumours accounted for 12.9% of all corpus uteri malignancies diagnosed at St. Luke's Hospital. There is little reliable comparable information available on endometrial cancer in different regions of the world. Information based on the International Classification of Disease⁽²²⁾ presented in figure 1 shows the Maltese population to have a high incidence of corpus uteri malignancies as compared to other European coun-

tries. There is however a wide incidence range between different populations, so that a very high (38.5) and a very low (1.7) incidence has been reported from U.S.A. (Albanea, white) and Japan respectively. The mortality rate from uterine malignancy in the Maltese Islands appears to be lower than in most other countries^(23, 24). There appears to be a slight difference in the incidence of endometrial carcinoma in the populations of the two main islands of the Maltese Archipelago. Thus during the period 1979-1983, there were 10 cases of adenocarcinoma from Gozo and 111 cases from Malta, giving an annual incidence of 16.1 and 14.9 per 100,000 female population respectively. The increased incidence for Gozo may be a result of a more elderly population on the island.

The incidence of uterine malignancy in the Maltese population has varied considerably in the last 20 years. Figure 2 shows a rise after 1965 followed by a gradual downward trend reaching an incidence of 5.0 per 100,000 female population. After 1977, there was again a sharp rise to levels of 19.2 per 100,000 females. The incidence has since persisted at around this level. A similar rise in incidence rates of endometrial carcinoma has been noted for other countries⁽¹⁴⁾. It is difficult to explain the rise in the incidence after 1977, especially when compared to the mortality rates from uterine malignancies which appear to follow a gradual downward trend (figure 2). Misinterpretation of some complex hyperplasias and metaplasias as carcinoma may partly account for the rise. The increased incidence may also be result of variations in the reporting of cases in different years. This may be partly confirmed by the similar patterns which may be noted in the incidence of cervical and breast malignancies.

The increase in the life expectancy of a population could possibly influence the

the elderly. While life expectancy has improved in the Maltese population, the differences are too small to account for the different incidence rates. Thus in 1961, 20.3% of women were over 50 years of age, while in 1981 this age group included 23.7% of the female population⁽³⁾. The age group distribution of the cases with endometrial adenocarcinoma during the period 1979-1983 confirms that the patients most at risk are aged over 60 years (table 1).

Table 1. — Age distribution of endometrial adenocarcinoma Maltese Islands 1979-1983.

Age (years)	Number of carcinoma cases	Maltese % distribution by age 1979-1983	Incidence per 100,000 female population
under 20	nil	30.14	nil
50 - 59	25	10.38	29.1
20 - 39	7	34.32	2.5
40 - 49	14	11.51	14.7
50 - 59	25	10.38	29.1
60 - 69	38	7.19	63.9
70 - 79	30	4.97	73.0
over 80	7	1.49	57.0
Total	121	100.0	14.6

CLINICAL ASSOCIATION

Discussions concerning the aetiology of endometrial adenocarcinoma have centered largely around the possible role of oestrogen in producing this malignancy. Such attention was inevitable given the known proliferative effect oestrogen has on the endometrium, and the association of endometrial hyperplasia with prolonged unopposed oestrogen stimulation. There is a considerable body of circumstantial evidence to implicate both endogenous and exogenous oestrogens in the evolution of endometrial carcinoma⁽⁸⁾. Much of this evidence is related indirectly to a number of clinical features which have been sta-

tistically correlated to be associated with endometrial adenocarcinoma.

Obesity

The most common clinical correlate of endometrial carcinoma is obesity with a reported incidence of 21 to over 80% (10). In the study population, 50% of the patients were identified by the clinicians attending the cases as being obese. How-

ever obesity is one of the most important socio-medical problems effecting the Maltese population. More than 60% of the male population, and an even higher percentage of females suffer from excessive body weight (21). Life style and nutritional factors in the induction of cancer have been the subject of many investigations (20). Body weight at the time of the menopause is correlated with postmenopausal endometrial adenocarcinoma, and obesity has been suggested to be the most important factor in the induction of endometrial cancer (25). Armstrong and Doll (1) related the incidence of endometrial cancer to national levels of dietary fat consumption and concluded that dietary fat or calorie level is a significant factor in determining the individual's risk of developing endometrial adenocarcinoma. The Maltese consume large amounts of food with an average energy intake in females of about 6.5 MJ. Total fat account for

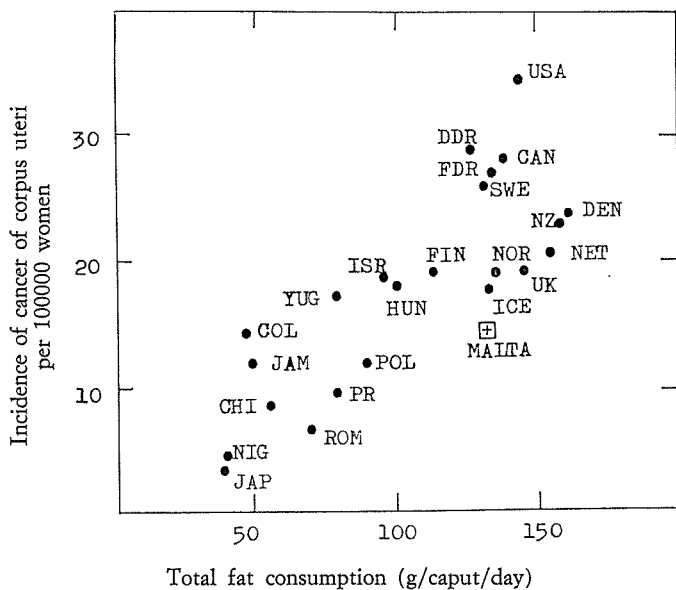


Fig. 3. — Correlation between incidence of cancer corpus uteri and total consumption. (After: Armstrong and Doll, 1975 and data from Malta after Vuksan, 1984 and present series).

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approximately 45.6% of this intake (21). The incidence of endometrial carcinoma correlated to the total fat consumption of the population (figure 3) compares favourably with the correlation identified by Armstrong and Doll (1). The biochemical role of obesity in the aetiology of endometrial carcinoma has been attributed to aromatization of circulating androstenedione in adipose tissue (11) accounting for the elevated oestrogen excretion in the obese woman (15). Similarly elevated peripheral blood levels of oestrone have been re-

ported in women with overt diabetes mellitus⁽⁵⁾.

Diabetes mellitus

It has frequently been suggested that diabetes mellitus may be associated with an increased endometrial cancer risk, though the reports are conflicting. Mac Mahon⁽¹³⁾ reported a relative risk of 2.8 associated with a history of diabetes even after controlling for age, body weight and socio-economic status. The Maltese Islands have been shown to have a high prevalence of diabetes mellitus and impaired glucose tolerance as compared to other countries. The prevalence of diabetes mellitus in women aged 45 years or more ranges between 14-29% depending on the age group⁽¹⁶⁾. This high prevalence may in part account for the higher incidence of endometrial carcinoma reported for the Islands. In the study population, 35.6% of the patients had a fasting blood glucose greater or equal to 7.0 mmol/l.

Hypertension

Another nutritionally related disease is hypertension, which has been correlated to high animal fat diets. Some studies have shown a positive association between endometrial cancer and hypertension, but the evidence is again conflicting^(13, 25). In the study population 71.2% of the cases were found to be hypertensive when first seen. In a random sample of 150 females aged more than 50 years attending the gynaecology clinic for conditions other than endometrial carcinoma, 61.3% were found to be hypertensive.

Other associated conditions

Other conditions may be responsible for the increased peripheral oestrogen formation from precursors, the process being more efficient again in women. Thus women with polycystic ovarian disease produce three to four times more androste-

nedione than normal women, and also greater peripheral quantities of oestrogen⁽¹⁷⁾. Tumours and hyperplasia of the ovarian stroma are also associated with increased androstenedione production⁽¹²⁾. Patients with these conditions have been reported to have an increased risk of endometrial hyperplasia and adenocarcinoma⁽⁷⁾, though the incidence of these disorders with endometrial adenocarcinoma in the study population appears to be low (table 2). An association with uterine leiomyomas has also been described and related to the suggestion that oestrogens may be important in the development and maintenance of leiomyomas. Oestradiol levels are sometimes increased in women with leiomyomas, and one study⁽⁶⁾ has shown that the smooth muscle cells in leiomyomas will bind oestradiol.

Uterine smooth muscle tumours were present in 11.5% of cases in the study population (table 2). The annual incidence of histologically proved uterine smooth muscle tumours in the Maltese population aged over 20 years is about 104 per 100,000, the majority being in the 40-49 years age group. The annual incidence of malignant uterine smooth muscle tumours is about 2.5 per 100,000 female population aged over 20 years. Maltese females with histologically diagnosed uterine

Table 2. — *Associated conditions with endometrial carcinoma Maltese Islands 1979-1983.*

Associated conditions	No.	%
Uterine smooth muscle tumors ⁽¹⁾	12	11.5
Ovarian cysts/tumours ⁽²⁾	10	9.6
Breast carcinoma	2	1.9
Thyroid disease	2	1.9
Other disorders ⁽³⁾	5	4.0

(1) one case of leiomyosarcoma

(2) one case of oestrogen secreting granulosa cell tumour, and one case of adenocarcinoma

(3) single cases of stomach leiomyoma, forehead basal cell carcinoma, and endometriosis. Two cases of adenomyosis.

Table 3. — Parity distribution of endometrial adenocarcinoma Maltese Islands 1979-1983.

Parity	No.	%
P0	48	46.2
P1	4	3.9
P2	7	6.7
P3	9	8.7
P4	7	6.7
P5	29	27.8
Total	104	100.0

smooth muscle tumours had a 1.4% chance having an associated endometrial carcinoma⁽¹⁸⁾. A correlation to endometrial adenocarcinoma has been described for long-term oestrogen therapy⁽¹⁰⁾, though there is no evidence that combined oral contraceptives are associated with an altered incidence of endometrial neoplasia.

Progestogens have been shown to reverse both spontaneously arising and oestrogen induced endometrial hyperplasia, and to have a protective effect against the development of adenocarcinoma. This action is probably a result of an antioestrogen effect on uterine epithelial cells⁽⁸⁾.

Patients with endometrial carcinoma have also been reported as having a history of dysfunctional uterine bleeding or secondary amenorrhoea, often reported to be the result of anovulation. Additionally, these patients are relatively infertile and of low parity. While a previous history of dysfunctional uterine bleeding was difficult to establish in the study population, 46.2% were found to be nulliparous confirming previous findings. High fertility however is not completely exclusive of endometrial carcinoma, so that 27.8% of the cases had five or more children (table 3). The correlation between nulliparity and endometrial adenocarcinoma does not appear to be related to anovulation alone, since of the 48 patients who were nulliparous 56.3% were unmarried and had never attempted to get pregnant. There have been some suggestions that different

forms of oestrogens may have carcinogenic or protective effects. One theory proposes that oestriol may protect against breast and endometrial cancer⁽⁹⁾. This theory was based on the observation that breast cancer and endometrial cancer patients have lower oestriol: oestrone and oestradiol ratios than normal postmenopausal women. Since oestriol levels are known to increase during pregnancy, multiparous women may have a lower risk of developing breast or endometrial cancer. Breast cancer has been related to uterine adenocarcinoma⁽²⁾ and shown to have similar risk factors. This relationship may however be fortuitous since both conditions are common in the female population. The study population revealed two cases (1.9%) of uterine adenocarcinoma who had breast malignancy confirmed previously. The incidence of breast carcinoma in the Maltese female population is about 0.05%. Thyroid dysfunction has also been correlated with endometrial carcinoma, possibly by interfering with the cholesterol mechanism⁽¹⁹⁾. Only two cases of the study population had a previous history of thyroid disease, both patients were euthyroid.

CONCLUSION

The fundamental purpose of epidemiology is not only to uncover new information about aetiologies, but to determine measures which may contribute to the decline in the incidence of the disease. It would appear that a number of risk factors may be associated with the aetiology of endometrial carcinoma. Rarely does one encounter a patient with endometrial carcinoma who does not present at least one of the disorders that constitute the "cancer triad", i.e. obesity, diabetes mellitus and hypertension.

Preventive action can be considered for patients at risk, thus helping decrease the incidence of endometrial carcinoma, parti-

cularly if related to a high animal fat diet. It therefore becomes desirable to avoid or reduce obesity to decrease the risk of endometrial adenocarcinoma. Presumably the earlier the weight reduction, the better the prognosis.

Oestrogen replacement therapy offers risks and benefits. The benefits appear to be in the relief of specific symptoms of hypoestrogenism. These include vasomotor hot flushes and atrophic vaginitis. There is also evidence that oestrogens reduce the incidence of certain metabolic disorders, such as cardiovascular disease and osteoporosis. The increased risk of endometrial cancer is at present the most important known drawback to the use of non-contraceptive oestrogen preparations. Available data suggest that this risk can be lessened by the use of a progestogen in oestrogen-treated postmenopausal women, as well as those at high risk for developing endometrial adenocarcinoma.

The identification of high risk groups facilitates screening efforts directed at the population at risk. A variety of instruments for endometrial sampling on an outpatient basis have been described. The approaches to endometrial diagnostic sampling can be classified into two groups: examination of tissue samples and cytologic procedures. The diagnostic efficacy of the endometrial biopsy instruments is adequate, but difficult to use for screening purposes. Although cytologic samples obtained by various methods are helpful in screening a large number of patients, a high false-negative rate limits the usefulness of cytology in diagnosing endometrial carcinoma and pre-cancerous lesions.

The immediate investigation of women with abnormal vaginal bleeding would seem to be the most practical means of improving the end results in this disease at the present time. Complete evaluation of a case with abnormal uterine bleeding in the perimenopausal and postmenopausal age groups should include dilatation and

fractional curettage to establish the diagnosis.

The majority of cases of endometrial adenocarcinoma generally present early in the course of the disease. However although unproved, it appears likely, that at least some patients who are first seen with a prognostically unfavourable advanced stage of the disease had an asymptomatic stage of tumour development. Therefore, the question of feasibility of screening for endometrial cancer in suitably identified target populations must be raised and needs to be investigated further.

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