Endocrinopathy Associated with Pancreatic Carcinomas

Review of Host Factors Including Hyperplasia and Gonadotropic Activity

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PANCREATIC duct epithelium proliferates in response to hormonal stimuli and in the presence of certain neoplasms. Hyperplasia of pancreatic ducts has been induced in rabbits and hamsters by administering somatotropin and in mice by grafting pituitary tumors that secrete thyrotropin and gonadotropins.[2, 5] In man ductal hyperplasia frequently accompanies adenocarcinoma of the pancreas, colon and lung.[5, 7] Cystadenomas of pancreatic duct cell origin commonly occur in conjunction with other primary neoplasms and various endocrinopathies.[4]

If the factors that operate to produce *hyperplasia* and *cystadenoma* of pancreatic duct epithelium are also implicated in the production of carcinoma, it might be expected that patients with pancreatic carcinoma would display a similar array of associated endocrinopathies and tumors. To test this hypothesis a host profile analysis has been performed.

Materials and Methods

One hundred and twenty autopsied cases of pancreatic duct cell carcinoma and 120 concurrently autopsied age and sex matched non-cancer control cases were collected, chiefly from the New England Deaconess Hospital, Peter Bent Brigham Hospital and Pondville Hospital in Massachusetts. Cases were excluded from the study either if the clinical or pathologic material was considered inadequate or if there was ambiguity concerning the origin of the pancreatic tumor. Morphologic correlations of *gonadotropic activity* were evaluated in women by estimating the thickness of the ovarian cortical stroma, and the status of the endometrium, cervix and breast. In men, sections of prostate and testis were examined and indices of *spermatogenic hypertrophy* calculated. Methods utilized have been described previously.[3, 6]

Results

The series included 73 men (61 per cent) and 47 women (39 per cent) whose ages ranged from 34 to 86 years. The modes occurred in the seventh and eighth decades among men and women, respectively. The median age at death was 65 years for both sexes.

Mean height among men with cancer was 65 inches (controls 68 inches), and among women 63 inches (controls 61 inches). Mean weight prior to the onset of terminal illness was 164 lb. for men (controls 165 lb.) and 144 lb. for women (controls 136 lb.).

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TABLE 1. *Summary of Non-Cancerous Endocrine Abnormalities in Patients with Pancreatic Cancer*

	Cancer			Control		
	No. Cases	Total	%	No. Cases	Total	%
Females						
Ovarian cortical stromal hyperplasia	18	28	64	14	34	41
Endometrial hyperplasia	11	33	33	5	38	13
Uteri with myomata	10	33	30	4	38	11
Remote hysterectomy for benign disorder	6	47	13	5	47	11
Ovary neoplasm, benign	5	47	11	0	47	0
Fibroma—2						
Thecoma—1						
Cystic teratoma—1						
Papillary cystadenoma—1						
Uterine polyps	6	33	18	6	38	16
Uterine cancer	4	—	—	—	—	—
Diabetes mellitus	12	47	26	6	47	13
Males						
Index of spermatogenic hypertrophy*		32	1.69 ±0.21		43	2.08 ±0.16
Decreased or absent spermatogenesis	27	43	63	35	46	76
Prostatic hyperplasia	34	61	56	24	53	45
Prostatic atrophy	18	61	30	8	53	15
Diabetes mellitus	15	73	21	6	73	8

* $p > 0.05$.

Non-cancerous abnormalities of the endocrine glands and target organs are summarized in Table 1. Among the women with pancreatic cancer ovarian cortical stromal hyperplasia was present in 64 per cent of ovaries examined (controls 41 per cent), endometrial hyperplasia in 33 per cent (controls 13 per cent), and uterine myomata in 30 per cent (controls 11 per cent). Five women in the cancer group had benign ovarian neoplasms, whereas none were observed among the controls.

Among the men with pancreatic cancer 63 per cent of testes examined microscopically showed decreased or absent spermatogenesis (controls 76 per cent). Indices of spermatogenic hypertrophy averaged 1.69 ± 0.21 (controls 2.08 ± 0.16, $p > 0.05$). Indices in excess of 3.0 were observed only four times in patients with cancer, as compared to 12 times in controls. Prostatic hyperplasia occurred in 56 per cent of the cancer group (controls 45 per cent), and atrophy in 30 per cent (controls 8 per cent). In many glands the two processes coexisted.

Clinical or pathologic evidence of *diabetes mellitus* was present in 21 per cent of men with cancer (controls 8 per cent) and 26 per cent of women (controls 13 per cent).

Of the 97 thyroid glands examined in the cancer groups there were 11 non-toxic nodular goiters (11 per cent), five benign adenomas (four of follicular type and one Hurthle cell adenoma) and two diffuse hyperplasias. Of 104 control glands there were eight non-toxic nodular goiters (7 per cent), one Hurthle cell adenoma and three diffuse hyperplasias.

Adrenal sections were reviewed in 112 cancer patients and 114 controls. They were evaluated with particular reference to parameters of ACTH effect: cortical thickness and nodularity. Abnormal cortical thickening was present in 16 per cent

TABLE 2. *Distribution of 33 Extrapancreatic Cancers Among 120 Patients With Pancreatic Duct Cell Carcinoma*

Males		Females	
Carcinoma of prostate	9	Carcinoma of breast	3
Carcinoma of thyroid	1	Adenocarcinoma of uterus	2
Adenocarcinoma of colon	2	Leiomyosarcoma of uterus	2
Cecum 1			
Rectum 1		Carcinoma of thyroid	1
Carcinoma of bladder	1	Carcinoma of gallbladder	3
Monocytic leukemia	1	Epidermoid carcinoma of nasopharynx	1
Hodgkin's disease	1		
Renal cell carcinoma	1		
Basal cell carcinoma of skin of face	1		
Melanoma of penis	1		
Epidermoid carcinoma of pharynx	1		
Chondrosarcoma of forearm	1		
Undifferentiated retroperitoneal sarcoma	1		
Total	21	Total	12

of adrenals from cancer patients and 11 per cent of controls. Nodularity occurred in 51 and 54 per cent of the cancer and control glands, respectively. Four per cent of both the cancer and control groups had cortical adenomas.

Pituitary and parathyroid glands were examined only in a small minority of cases. Various abnormalities were present but without any consistent pattern.

Multiple primary malignant tumors occurred in 19 men (26 per cent) and nine women (20 per cent). One man had four, and three women each had three primary cancers. Eighteen (55 per cent) of these total 33 extrapancreatic cancers occurred in primary endocrine target organs. There were nine cancers of the prostate, four of the uterus (two adenocarcinomas and two leiomyosarcomas), three of the breast and two of the thyroid (Table 2). The combination of cancer of the gallbladder and pancreas with proliferative disorders of the endometrium and ovary was found three times, and cancers of the breast, uterus and pancreas occurred together twice (Table 3).

Discussion

Malignant extrapancreatic tumors were observed in 23.3 per cent of the 120 patients with pancreatic duct cell carcinoma. In a parallel study of 2,829 unselected cancer autopsies Warren and Gates[8] reported a 6.8 per cent incidence of multiple primary cancers. The threefold difference between these two figures suggests a tumor diathesis. A similar situation has been noted in patients with pancreatic cystadenomas.[4]

The sex distribution of the 33 extrapancreatic malignant tumors is shown in Table 2. Among women the predilection of these tumors for the secondary sex organs, and the high incidence of ovarian cortical stromal and endometrial hyperplasia suggest excessive gonadotropic and secondarily estrogenic stimulation. In each of the three cases in which cancers of the pancreas and gallbladder coexisted the ovaries showed cortical stromal hyperplasia. This constellation might be fortuitous or it may represent a generalized response of the pancreatic-biliary duct system mediated in part by gonadotropic hormones.

TABLE 3. *Survey of Endocrine Abnormalities Among 9 Women With Pancreatic Duct Cell Carcinoma and Multiple Primary Malignancies*

Case No.	Age at Death	Location of Extrapancreatic Cancers	Breast	Ovaries	Uterus	Adrenals	Thyroid	Other
1	79	Gallbladder	Adenofibrosis	Thecomatosis Cortical stromal hyperplasia	Adenomatous and cystic hyperplasia	Not remarkable	Fetal adenoma	
2	74	Breast	Carcinoma	Surgically absent	Surgically absent	Striking hyperplasia of zona fasciculata	Adenomatous goiter	
3	70	Breast Uterus	Carcinoma	Papillary cystadenoma Cortical stromal hyperplasia	Endometrial polyp Leiomyosarcoma	Unusually nodular and rich in lipoid	Hurthle cell adenoma Adenomatous goiter	Usual weight 240 lb.
4	65	Gallbladder	No data	Cortical stromal hyperplasia	Not remarkable	Not remarkable	Nodular	
5	54	Uterus	No data	Surgically absent	Adenocarcinoma (Surgically absent)	Nodular thickening of zona fasciculata	No data	
6	52	Breast Uterus	Carcinoma	Cortical stromal hyperplasia	Cystic hyperplasia Leiomyosarcoma	Cortical adenoma	Not remarkable	
7	53	Gallbladder	Adenofibrosis	Cortical stromal hyperplasia	Atypical hyperplasia Adenocarcinoma (*in situ*)	Nodular cortex of usual width	Chronic thyroiditis with many Hurthle cells	Obese
8	69	Thyroid	No data	Cortical stromal hyperplasia Ovarian cyst (Surgically removed)	Endometrial polyp Leiomyoma	Irregular nodularity of zona fasciculata	Carcinoma	Nodular chromophobe hyperplasia of pituitary
9	70	Nasopharynx	No data	Surgically absent	Surgically absent	Not remarkable	Adenomatous goiter (previously operated upon)	Chromophobe adenoma of pituitary

Among men with pancreatic cancer there were no unusual sexual apparatus alterations. The nine prostatic cancers represent an incidence of 13 per cent, within the expected range for middle-aged men.[1] All the prostatic cancers were microscopic and subclinical. None metastasized. Comparisons of testes and prostates in the cancer and non-cancer control groups showed slightly better spermatogenesis among the men with cancer and slightly lower indices of spermatogenic hypertrophy. The latter were not statistically significant.

Abnormalities of the nonreproductive endocrine glands included a high incidence of diabetes mellitus. This has been noted previously in patients with pancreatic duct cell carcinomas[5] and also with pancreatic cystadenoma.[4] Benign tumors of the thyroid were rather common. The adrenals were essentially similar in both cancer and non-cancer control groups.

Summary

Constitutional abnormalities were analyzed in 120 autopsied cases of pancreatic duct cell carcinoma and 120 non-cancer controls that were age and sex matched. Men outnumbered women in a ratio of 1.6:1. Among women with pancreatic cancer there was an increased incidence of

ovarian cortical stromal and endometrial hyperplasia. Neoplasms of the gallbladder, breast, ovary and uterus were also relatively frequent. Among affected men the reproductive organs were similar in both the cancer and control groups. Diabetes mellitus and thyroid neoplasms were common in both the male and female pancreatic cancer groups. The data suggest that among women but not men with pancreatic duct cell carcinoma there is excessive gonadotropic hormone activity.

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