MINI-REVIEW

A Review of Cohort Studies on the Association Between History of Diabetes Mellitus and Occurrence of Cancer

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Abstract

We conducted a review of previous cohort studies on the association between a history of diabetes mellitus (DM) and the occurrence of cancer. We limited the papers to those concerning cohort studies on 9 cancer sites, i.e. the kidney, liver, biliary tract, pancreas, colon or rectum, prostate, breast, endometrium, and ovary, in addition to all cancers. With regard to kidney, liver, biliary tract, pancreatic, colorectal, breast, and endometrial cancers, the risk of cancer development has been consistently reported to be positively associated with DM by two or more cohort studies. In contrast, DM was shown to relate negatively to the risk of prostate cancer by two cohort studies. However, there were no cohort studies which showed an either significantly positive or negative association of DM with ovarian cancer. Elevated levels of insulin or IGFs among DM patients have been proposed as a causal mechanism of increased risk for most of the reviewed cancers. In addition, increased estrogen levels in DM patients have been suggested to explain the casual mechanism of increased risk for kidney, breast and endometrial cancers, and decreased risk for prostate cancer. On the other hand, the possibility of detection bias has been suggested in the association of DM with the risk of most of these cancers. Obesity and heavy consumption of alcohol have been indicated as confounding factors in the relationship of DM to the risk for some of them. Thus, further studies are necessary for firm conclusions regarding the association of DM with cancer risk.

Key words: diabetes mellitus - cohort studies - cancer - kidney -liver - biliary tract - pancreas - colorectum - prostate - breast - endometrium

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Introduction

Diabetes mellitus (DM) is a metabolic disease with two major subtypes (insulin-dependent and non-insulin-dependent) that is characterized by abnormalities in the synthesis and cellular uptake of insulin. As shown in Figure 1, the prevalence of patients with DM has been gradually increasing in Japan (Statistics and Information Department, Ministry of Health and Welfare, 1999). It has been reported that more than 15% and 5% of Japanese aged 40 years or over suffer from impaired glucose tolerance and DM, respectively (Sasaki et al., 1998). These phenomena may be explained by recent changes in the lifestyle of the Japanese, especially, increased energy intake and decreased physical activities.

It is well recognized that DM is a risk factor for fatal circulatory diseases such as coronary heart disease and stroke (D'Agostino et al., 1994, Adlerberth et al., 1998, Tominaga et al., 1999). In addition, many reports have suggested that a history of DM is a risk factor for cancer

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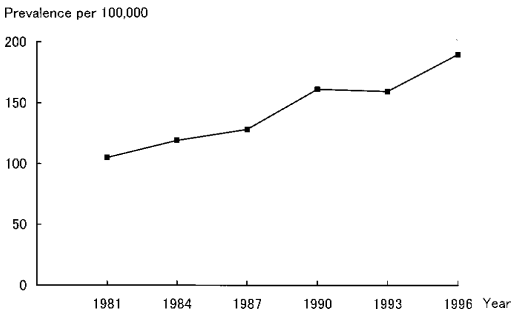

Figure. Secular Trend of Prevalence of Diabetes Mellitus in Japan

of such sites as the kidney, liver, biliary tract, pancreas, colon, rectum, breast, and endometrium. Incidences of most of these cancers have been rising in Japan as well (Fujimoto et al., 1993).

Since we recently started a cohort study to assess the association between DM and the occurrence of cancer in Hokkaido, Japan, financially supported by the Ministry of Education, Science, Sports and Culture of Japan, we conducted a review of previous cohort studies on this association. We also discuss the etiological considerations of the association.

Review Process

We utilized MEDLINE for a computer-oriented systematical search of articles of cohort studies on the association between DM and the occurrence of cancer. For reviewing the association with DM, we limited the papers to those concerning cohort studies on 9 cancer sites, i.e. the kidney, liver, biliary tract, pancreas, colon or rectum, prostate, breast, endometrium, and ovary, in addition to all cancers (cancers combined in all sites). There are some published cohort studies that assessed the association of DM with the risk for each of these cancers. We also restricted the reviewed papers to those published after 1980 and written in English. According to the data of the Saga Prefectural Cancer Registry from 1988 to 1992 (Mori et al., 1997), the total proportions of these 9 cancers were 38.2% and 50.8% of all male and female cancers, respectively, of Japanese.

All Cancers

As shown in Table 1, 3 of 6 cohort studies on males and 2 of 5 cohort studies of males showed the weak, but significantly positive association between a history of DM and the occurrence of all cancers. Findings of most investigators have indicated an about 10% excess risk for all cancers among those with DM.

Hypotheses put forward to explain the relationship between DM and cancer include; 1) a true etiological relationship between DM and cancer; 2) DM and cancer increase in people sharing common risk factors (e.g. obesity, heavy consumption of alcohol, other dietary factors); 3) increased cancer detection due to increased medical surveillance of diabetes; 4) malignancy causing an increase in the severity of subclinical DM (Ragozzino et al., 1982, Steenland et al., 1995).

Table 1. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to all Cancers Estimated from Cohort Studies

First author	Gender	RR	95% CI
Ragozzino (1982)	Males	1.2	0.9~1.5
	Females	1.1	0.8~1.4
Levine (1990)	(Plasma glucose per 50mg/dl)		
	Males	1.18*	1.05~1.31
	Females	0.92	0.77~1.09
Adami (1991)	Males	1.0	0.9~1.1
	Females	1.1*	1.0~1.1
Smith (1992)	Males	0.97	0.92~1.03
Wideroff (1994)	Males	1.1*	1.1~1.1
	Females	1.1*	1.1~1.1
Steenland (1995)	Males	1.38*	1.00~1.91
	Females	1.14	0.81~1.62

*: P<0.05

Supporting an etiological association of DM with cancer, Adami et al. (1991), suggested that immunologic, metabolic, or hormonal abnormalities characteristic of the DM state may promote the development of cancer in susceptible individuals. Furthermore, Dandona et al. (1996) showed that DM patients exhibited greater oxidative damage to DNA than the non-DM controls as measured by the concentration of 8-hydroxy-deoxyguanosine in mononuclear cells. Such changes may directly contribute to neoplastic complications in DM patients.

However, it is possible that the relationship of DM with cancer risk may be different by cancer site. Accordingly, we reviewed the papers of cohort studies on this association by cancer site, as follows.

Cancer by Site

a) Kidney cancer

As shown in Table 2, 2 out of 4 cohort studies involving men and 3 out of 3 cohort studies with women showed the significantly positive association between DM and occurrence of kidney. Kidney cancer accounts for 1.8% and 1.4% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates of the cancer were 4.9 and 1.9 per 100,000 person-years of males and females there, respectively (Mori et al., 1997). Renal cell cancer accounts for most of the kidney cancer patients. Possible risk factors for renal cell cancer, besides DM, include cigarette smoking, hypertension, use of diuretics or other antihypertensives, use of analgesics like phenacetin, obesity, meat

Table 2. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Kidney Cancer Estimated from Cohort Studies

First author	Gender	RR	95% CI
Adami (1991)	Males	1.1	0.8~1.4
	Females	1.6*	1.2~2.0
Coughlin (1997)	Males	0.99	0.46~2.13
Wideroff (1997)	Males	1.4*	1.2~1.6
	Females	1.7*	1.4~1.9
Lindblad (1999)\	Males	1.3*	1.1~1.6
	Females	1.7*	1.4~2.0

*: P<0.05

consumption, and other dietary factors (Coughlin et al., 1997).

Renal cell cancer development in DM patients could be related to hormonal changes (Lindblad et al., 1999). Endogenous estrogens influence the development of renal cell cancer, and women with DM have been reported to have high levels of endogenous estrogens. Furthermore, raised growth factors such as insulin-like growth factor-1 (IGF-1) and growth factor receptors may be involved in the development of renal cell cancer among DM patients (Lindblad et al., 1999).

Although DM may be a risk factor for renal cell cancer, it remains unclear whether DM is an independent causal factor or an intermediate step in the causal link between a predisposing condition (e.g. obesity, hypertension) and renal cell cancer.

b) Liver cancer

As shown in Table 3, 2 cohort studies showed a significantly positive association between DM and occurrence of liver cancer in males as well as females. Liver cancer accounts for 14.9% and 9.3% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates of the cancer were 41.0 and 11.3 per 100,000 person-years for males and females there, respectively (Mori et al., 1997). Hepatocellular carcinoma accounts for most of the liver cancer patients. Recognized risk factors for hepatocellular carcinoma, besides DM, are hepatitis B or C virus infection, ingestion of food contaminated with aflatoxin, heavy consumption of alcohol, and habitual smoking.

Table 3. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Liver Cancer Estimated from Cohort Studies

First author	Gender	RR	95%CI
Adami (1996)	Males	4.7*	4.2~5.2
	Females	3.4*	2.9~3.9
Wideroff (1997)	Males	4.0*	3.5~4.6
	Females	2.1*	1.6~2.7

*: P<0.05

Growth-promoting effects in the liver might occur through stimulation of insulin and IGF receptors as a consequence of elevated circulating levels of insulin or its precursors among DM patients (Adami et al., 1996). Through another mechanism, the liver of DM patients may undergo fatty changes with the potential for necrosis, resulting in liver cancer (Wideroff et al., 1997).

A third common factor such as heavy consumption of alcohol may be involved as a risk factor for both DM and liver cancer (Wideroff et al., 1997). However, an association may arise spuriously if DM patients are more likely to be screened for liver disease than those without DM.

c) Biliary tract cancer

As shown in Table 4, 2 out of 3 cohort studies showed a significantly positive association between DM and the occurrence of cancer of the biliary tract, including the gallbladder and extrahepatic bile duct, in both males and females. Biliary tract cancer accounts for 3.0% and 6.4% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates of the cancer were 7.7 and 7.8 per 100,000 person-years for males and females there, respectively (Mori et al., 1997). Recognized risk factors for gallbladder cancer, besides DM, are gallstones and obesity.

According to Adami et al. (1996), in DM patients, gallbladder emptying is reduced, promoting biliary stasis and bacterial overgrowth that, in turn, promote the development of gallstones. The association, if confirmed, is probably mediated by the risk of gallstones reported in patients with DM, since gallstones are associated with an excess risk for cancers of the biliary tract. In another pathway, DM may be functioning as a marker of obesity, and obesity is a possible risk factor for gallbladder cancer.

Table 4. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Biliary Tract Cancer Estimated from Cohort Studies

First author	Gender	RR	95%CI
Ragozzino (1982)	(Gallbladder cancer)		
	Males	2.0	0.1~11.1
	Females	0.4	0.0~2.4
Adami (1996)	(Gallbladder cancer)		
	Males	1.2	0.9~1.7
	Females	1.4*	1.1~1.6
	(Extrahepatic bile duct cancer)		
	Males	1.6*	1.1~2.4
	Females	1.2	0.9~1.7
Wideroff (1997)	Males	1.4*	1.0~1.9
	Females	1.4*	1.1~1.5

*: P<0.05

Table 5. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Pancreatic Cancer Estimated from Cohort Studies

First author	Gender	RR	95% CI
Ragozzino (1982)	Males	3.8*	1.2~9.0
	Females	4.4*	1.2~11.4
Green (1985)	Total	2.53*	1.2~11.4
Mills (1988)	Total	3.76*	1.70~8.31
Hiatt (1988)	Total	4.5*	1.2 ~16.7
Adami (1991)	Males	1.4*	1.1 ~1.8
	Females	1.5*	1.2 ~1.8
Smith (1992)	Males	5.27*	1.90~14.60
Balkau (1993)	Total	3.3	0.98~12.0
	(Impaired glucose tolerance)		
	Total	1.6	0.45~5.3
Shibata (1994)	Total	2.37*	1.13~4.99
Chow (1995)	Total	2.08*	1.75~2.46
Wideroff (1997)	Males	1.7*	1.5~2.0
	Females	1.6*	1.4~1.9

*: P<0.05

d) Pancreatic cancer

As shown in Table 5, 9 of 10 cohort studies showed a significantly positive association between DM and the occurrence of pancreatic cancer in males, females, or combined subjects. Pancreatic cancer accounts for 3.8% and 4.8% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates of the cancer were 9.5 and 5.5 per 100,000 person-years for males and females there, respectively (Mori et al., 1997). Recognized risk factors for pancreatic cancer, besides DM, are smoking and diets high in red meat and cholesterol. Diets high in vegetables and fruits are probably protective against pancreatic cancer.

A plausible explanation for the causal relationship between DM and pancreatic cancer is the effect of insulin as a growth factor, which has been documented for a human pancreatic cell line (Balkau et al., 1993). In another mechanism, DM may be a marker of long-term pancreatic dysfunction, which results in the chronic stimulation of glandular cells and eventually in carcinogenic transformation (Shibata et al., 1994).

Another possibility is that both DM and pancreatic cancer share a common risk factor such as heavy consumption of alcohol (Balkau et al., 1993). A temporal sequence in which the diagnosis of diabetes precedes the diagnosis of pancreatic cancer has not yet been uniformly established (Wideroff et al., 1997); that is, DM might be an early manifestation of some pancreatic cancers that were diagnosed during the early years of follow-up. Furthermore, symptoms of pancreatic cancer may lead to the diagnosis of subclinical DM. However, Chow et al. (1995) stated that these phenomena could not easily explain the excess risk that persists for more than a decade after the initial hospitalization for DM.

e)Colorectal cancer

As shown in Table 6, 5 of 9 cohort studies showed a significantly positive association between DM and the occurrence of colorectal cancer in males, females, or combined subjects. Among the 5 articles that showed a significant association with DM, three were with colorectal cancer, one was with colonic cancer, and another was with rectal cancer. Colorectal cancer accounts for 11.6% and 14.5% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates for the cancer were 30.9 and 19.5 per 100,000 person-years for males and females there, respectively (Mori et al., 1997). Recognized risk factors for colorectal cancer, besides DM, are obesity, lack of physical activity, having a first-degree relative with colorectal cancer as a genetic predisposition, and consuming a high-fat or low-fiber diet, red meat, or processed meat. Diets high in vegetables decrease the risk of the cancer.

Table 6. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Colorectal Cancer Estimated from Cohort Studies

First Author	Gender	RR	95% CI
Ragozzino (1982)	(Colorectal cancer)		
	Males	1.4	0.7~2.5
	Females	1.3	0.5~2.1
Adami (1991)	(Colon cancer)		
	Males	1.2	0.9~1.4
	Females	1.0	0.8~1.2
	(Rectum cancer)		
	Males	1.3*	1.1~1.7
	Females	0.9	0.7~1.2
Smith (1992)	(Colon cancer)		
	Males	0.62	0.09~4.47
	(Rectum cancer)		
	Males	0.00	0.00~6.28
Kreger (1992)	(Colon cancer: Glucose intolerance)		
	Males	1.14	0.35~3.64
Steenland (1995)	(Colorectal cancer)		
	Males	1.43	0.61~3.31
	Females	1.40	0.64~3.10
Wideroff (1997)	(Colon cancer)		
	Males	1.3*	1.1~1.4
	Females	1.1*	1.0~1.2
	(Rectum cancer)		
	Males	1.1	0.9~1.2
	Females	1.0	0.9~1.2
Will (1998)	(Colorectal cancer)		
	Males	1.30*	1.03~1.65
	Females	1.16	0.87~1.53
Hu (1999)	(Colorectal cancer)		
	Females	1.53*	1.18~1.99
Schoen (1999)	(Colorectal cancer: 2-hour glucose level)		
	Total	2.4*	1.2~4.7
	(Colorectal cancer: 2-hour insulin level)		
		2.0*	1.0~3.8

*:P<0.05

It has been hypothesized that insulin and the IGF family may at high serum concentrations increase the risk of colorectal cancer by promoting growth of colorectal tumors, stimulating IGF receptors, and acting as a cell mitogen (Will et al., 1998, Hu et al., 1999, Schoen et al., 1999). According to Schoen et al. (1999), a recent nested case-control study found a statistically significant association between IGF-1 and colorectal cancer. Some other factors that might account for the higher colorectal cancer incidence among persons with DM are; 1) slower bowel transit, which contributes to increased exposure to toxic substances; 2) increased production of carcinogenic bile acids.

Obesity and lack of physical activities are potentially the most important confounders for the positive association between DM and colorectal cancer (Wideroff et al., 1997). Detection bias is the most plausible alternative explanation for the observed positive association because, among DM patients, early colorectal cancer may be more likely to be diagnosed as a result of heightened screening and detection.

f) Prostate cancer.

As shown in Table 7, 2 of 8 cohort studies showed a significantly negative association between DM and the occurrence of prostate cancer. Prostate cancer accounts for 2.9% of all male cancer patients in Saga Prefecture. The age-standardized incidence rate of the cancer was 6.7 per 100,000 person-years there (Mori et al., 1997). Recognized risk factors for prostate cancer are genetic predisposition, obesity, and regular consumption of animal fat or red meat. Diets high in vegetables are possibly protective against the cancer.

The inverse association between DM and risk of prostate cancer may be a result of alterations in sex hormone levels in DM patients. Higher testosterone levels have been associated with an increased risk of prostate cancer. This lower risk of prostate cancer may result from the adverse effect of glycemia on testicular Leydig cell function and testosterone secretion (Giovannucci et al., 1998). The plasma concentration of this hormone is decreased in adult men with DM and shows an inverse relationship to the degree of hyperglycemia. Furthermore, excessive concentrations of estrogens, which may suppress the growth of prostatic tumors, have been reported in men with DM (Adami et al., 1991).

Table 7. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Prostate Cancer Estimated from Cohort Studies.

First Author	RR	95% CI
Ragozzino (1982)	1.3	0.6~2.3
Green (1985)	1.57	0.66~3.75
Adami (1991)	0.7*	0.7~0.9
Smith (1992)	0.78	0.11~5.83
Steenland (1995)	1.45	0.78~2.71
Wideroff (1997)	0.9	0.8~1.0
Givovannucci (1998)	0.75*	0.59~0.95
Will (1999)	1.13	0.88~1.45

*:P<0.05

g) Breast cancer.

As shown in Table 8, 3 of 8 cohort studies showed a significantly positive association between a history of DM and the occurrence of breast cancer in females. One article assessed the association between a history of DM and the occurrence of male breast cancer, and did not indicate the significant one. Breast cancer accounts for 0.1% and 10.1% of all male and female cancer patients in Saga Prefecture, respectively. Age-standardized incidence rates of the cancer were 0.2 and 19.1 per 100,000 person-years of males and females there, respectively (Mori et al., 1997). Recognized risk factors for breast cancer, besides DM, are an early onset of menarche, low parity, late age at first birth, late natural menopause, long-term use of menopausal estrogen, obesity, and having a first-degree relative with breast cancer. Diets high in vegetables and fruits probably decrease the risk of the cancer, and diets high in fat and regular alcohol consumption possibly increase the risk.

Compared with healthy women, DM patients have been found to have higher levels of circulating estrogens, and a high level of estrogen is a possible etiological factor for breast cancer (Weiderpass et al., 1997, Goodman et al., 1997). In another pathway, insulin stimulates androgen synthesis in the ovarian stroma, and it decreases levels of sex hormone binding globulin (SHBG) and increases levels of free estradiol. According to Weiderpass et al. (1997), several studies have reported an inverse association between plasma levels of SHBG and breast cancer risk.

In women with DM, adipose tissue might

Table 8. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Breast Cancer Estimated from Cohort Studies.

First Author	Gender	RR	95% CI
Ragozzino (1982)	Females	1.3	0.7~2.2
Green (1985)	Females	0.69	0.29~1.66
Adami (1991)	Males	1.3	0.2 ~4.8
	Females	0.9	0.8 ~1.1
Sellers (1994)	Females	0.96	0.68~1.36
Steenland (1995)	Females	1.40	0.70~2.78
Goodman (1997)	Females	2.06*	1.27~3.34
Wideroff (1997)	Females	1.4*	1.2~1.6
Weiderpass (1997)	Females	1.8*	1.6~2.0

*P:0.05

Table 9. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus with Relation to Endometrial Cancer Estimated from Cohort Studies

First author	RR	95% CI
Ragozzino (1982)	1.5	0.3~4.4
Adami (1991)	1.5*	1.2~1.8
Wideroff (1997)	1.4*	1.2~1.6
Weiderpass (1997)	1.8*	1.6~2.0
Terry (1999)	1.6	0.2~11.3

*:P<0.05

synthesize higher levels of insulin and IGF-1, which are known growth-promoting hormones for normal breast epithelial cells and human breast cancer cells (Sellers et al., 1994). Another possibility is that insulin may exert a direct influence through estrogen receptors, altering the biologic behavior of steroid hormone target tissues (Weiderpass, 1997).

In view of the association between DM and obesity, breast cancer was elevated in the study of obesity and cancer. DM may function as a marker of a risk factor for breast cancer through its association with obesity.

h) Endometrial cancer

As shown in Table 9, 3 of 5 cohort studies showed a significantly positive association between a history of DM and occurrence of endometrial cancer. Endometrial cancer accounts for 3.9% of all female cancer patients in Saga Prefecture. Age-standardized incidence rates of the cancer were 2.3 per 100,000 person-years there (Mori et al., 1997). Recognized risk factors for endometrial cancer, besides DM, are low parity, exposure to exogenous estrogen commonly used in hormone replacement therapy, particularly without concurrent progesterones, and obesity. Diets high in vegetables and fruits probably reduce the risk of the cancer, and diets high in animal fat and cholesterol possibly increase the risk.

High levels of endogenous estrogens, a documented feature of women with DM and an established risk factor for endometrial cancer, is an explanation for such an association. Compared with healthy women, DM patients have been found to have higher levels of circulating estrogens in the post-menopausal period. Insulin may exert a direct influence through estrogen receptors, altering the biologic behavior of steroid hormone target tissues (Weiderpass, 1997). Another possibility is that DM may function as a marker of a risk factor for endometrial cancer through its association with obesity (Wideroff et al., 1997).

Table 10. Relative Risks (RRs) and their 95% Confidence Intervals (CIs) for History of Diabetes Mellitus for Ovarian Cancer Estimated from Cohort Studies

First author	RR	95% CI
Ragozzino (1982)	1.2	0.2~3.4
Adami (1991)	0.9	0.6~1.1
Wideroff (1997)	0.9	0.7~1.0

*:P<0.05

i) Ovarian cancer

As shown in Table 10, none of 3 cohort studies showed a significant association between a history of DM and the occurrence of ovarian cancer. Ovarian cancer accounts for 8.0% of all female cancer patients in Saga Prefecture. Age-standardized incidence rates of the cancer were 5.2 per 100,000 person-years there (Mori et al., 1997). Recognized risk factors for ovarian cancer

Table 11. Summary of Associations between History of Diabetes Mellitus and Risk of Cancer Reviewed by Published Articles

Cancer site	Association	Proposed Etiological Factors	Possible Confounding Factors	Possible Bias
Kidney	Positive	Increased growth factors including insulin /IGF-1 Increased estrogens.	Obesity, Hypertension	Detection bias
Liver	Positive	Increased growth factors including insulin /IGF-1 Fatty change of liver.	Heavy alcohol consumption	Detection bias
Biliary tract	Positive	Particular etiologic factors have not been proposed	Gallstone, Obesity	Detection bias
Pancreas	Positive	Increased growth factors including insulin /IGF-1	Heavy alcohol consumption	Symptom of cancer
Colon, Rectum	Positive	Increased growth factors including insulin /IGF-1 Slower bowel transit, Increased carcinogenic bile acids.	Obesity, Lack of physical activity.	Detection bias
Prostate	Negative	Reduced testosterone, Increased estrogens.	Obesity	
Breast	Positive	Increased estrogens, Increased growth factors including insulin /IGF-1.	Obesity.	Detection bias
Endometrium	Positive	Increased estrogens, Increased growth factors including insulin /IGF-1.	Obesity, Hypertension.	Detection bias
Ovary	Neither			

are low parity and genetic predisposition. Extended oral contraceptive use may decrease the risk of the cancer. Diets high in vegetables and fruits probably reduce the risk of the cancer, and diets high in animal fat and cholesterol possibly increase the risk.

Although none of the reviewed cohort studies showed a significant association of DM with the risk of ovarian cancer, several case-control studies, including ours (Mori et al., 1998), showed a significantly positive association. Additional cohort studies are necessary before concluding that a history of DM is not associated with the risk of ovarian cancer.

Summary

As Table 11 shows, in a summary of our review, in 7 of the 9 cancers examined, namely, kidney, liver, biliary tract, pancreatic, colorectal, breast, and endometrial cancers, the risk of cancer development has been consistently reported to be positively associated with DM by two or more cohort studies. In contrast, DM was shown to relate negatively to the risk of prostate cancer by two cohort studies. Furthermore, there were no cohort studies, as far as we reviewed, which showed an either significantly positive or negative association of DM with ovarian cancer.

Elevated levels of insulin or the IGFs among DM patients have been proposed to interpret a causal mechanism of increased risk for most of the reviewed cancers. On the other hand, increased estrogen levels in DM patients have been suggested to explain the casual mechanism of increased risk for kidney, breast and endometrial cancers, and decreased risk for prostate cancer. The possibility of detection bias has been suggested in the association of DM with the risk of most of these cancers. Obesity and heavy consumption of alcohol has been indicated as confounding factors in the relationship of DM to the risk for some of these cancers, as summarized in Table 11. Thus, further studies are necessary to elucidate the association of DM with cancer risk.

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Personal Profile: Mitsuru Mori

Education

1978 Graduate at Sapporo Medical University, School of Medicine
1978-1982 Graduate course at Department of Public Health, Sapporo Medical University, School of Medicine.

Employment Experience

1982-1984 Visiting Fellow at the National Institutes of Health in Bethesda.
1984-1990 Assistant Professor at Department of Public Health, Sapporo Medical University, School of Medicine.
1991-1992 Assistant Professor at Department of Public Health, Kurume University, School of Medicine.
1993-1999 Associate Professor at Department of Community Health Science, Saga Medical School.
1999-present Professor at Department of Public Health, Sapporo Medical University, School of Medicine.

Research Interests

Epidemiology of hormone-dependent cancers such as those in the ovary, endometrium, and prostate.

Personal Interests

Sports activities including jogging. This photograph of myself (left side) was taken at the Sapporo Healthy Marathon Festival in May, 2000, with Ms. Yuko Arimori, Barcelona Olympic Silver Medallist (1992), and Atlanta Olympic Bronze Medallist (1996) as a female marathoner.