Diyabette kanser biyolojisi Öncelik hangisinde?

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DIABETES AND CANCER*

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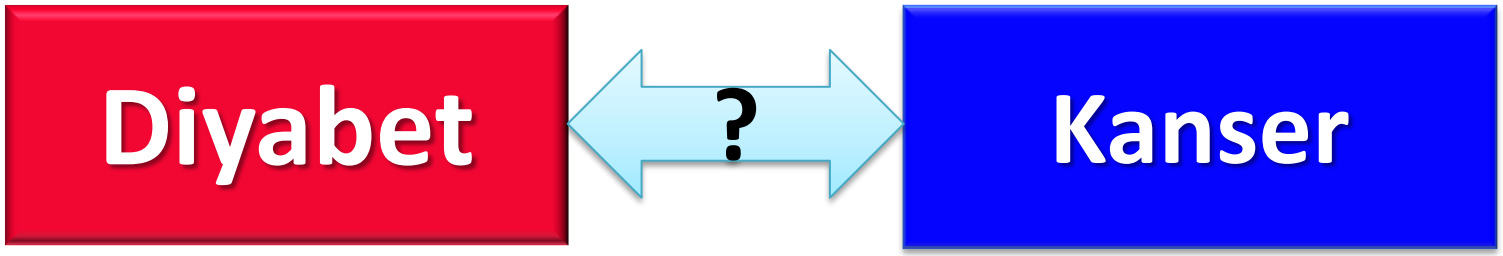
THE presence of diabetes and cancer in the same individual is an association which promotes speculation and calls for a consideration of the possible relationship between the two diseases. For this reason a study has been made of the records of approximately 10,000 patients with proved diabetes who were included in a series of 12,000 individuals of all ages coming for diagnosis or treatment of diabetes. Among this number, 256 cases of malignant disease, or approximately 2.6 per cent of the patients with true diabetes, are known to have occurred up to the present time. This proportion will undoubtedly increase considerably, because two-thirds of these 10,000 diabetics are still living and many of them will later develop cancer. Moreover, there are probably many unrecognized or unreported cancer cases, not only among deceased patients but also among those seven living. The summary in table I gives the findings in detail. The data as to age, duration of disease, etc., in the living cases are calculated as of September, 1933, except that patients known to have died since that date have been included as fatal cases.

Sex. Of the 219 fatal cases, ninety-four were males and 125 females. Of the thirty-seven living cases, eleven were males and twenty-six females. Thus, of the entire series, 59 per cent were females. This higher incidence among women is to be expected since both diabetes and cancer are more common in women than in men. Joslin[1] stated in 1928 that, since 1922, 55.2 per cent of his patients were females. Bigelow and Lombard[2] found that in 1929 and 1930, of cancer deaths in Massachusetts, 57.7 per cent were in women; in the U. S. Registration Area in 1929, 55.4 per cent of cancer deaths were in

- Marble 1934 yilinda diyabet ve kanser arasında bir ilişki olduğunu gösterdi
- Son 15 yılda bu ilişki giderek daha fazla tanındı


Diyabet
?
Kanser

Hiperglisemi ve kanser riski

Vasterbotten Intervention Project of Northern Sweden

- 33.293 K, 31.304 E, 2.478 kanser vakası
- 10 yıl sonra 10.000

	Açlık glukozu	P_{trend}	OGTT-2st glukoz	P_{trend}
Kadın	1.26 (1.09-1.47)	<0.001	1.31 (1.12-1.52)	<0.001
Erkek	1.08 (0.92-1.27)	0.26	0.98 (0.83-1.16)	0.99

Stattin P, et al. Diabetes Care 2007;30:561-67

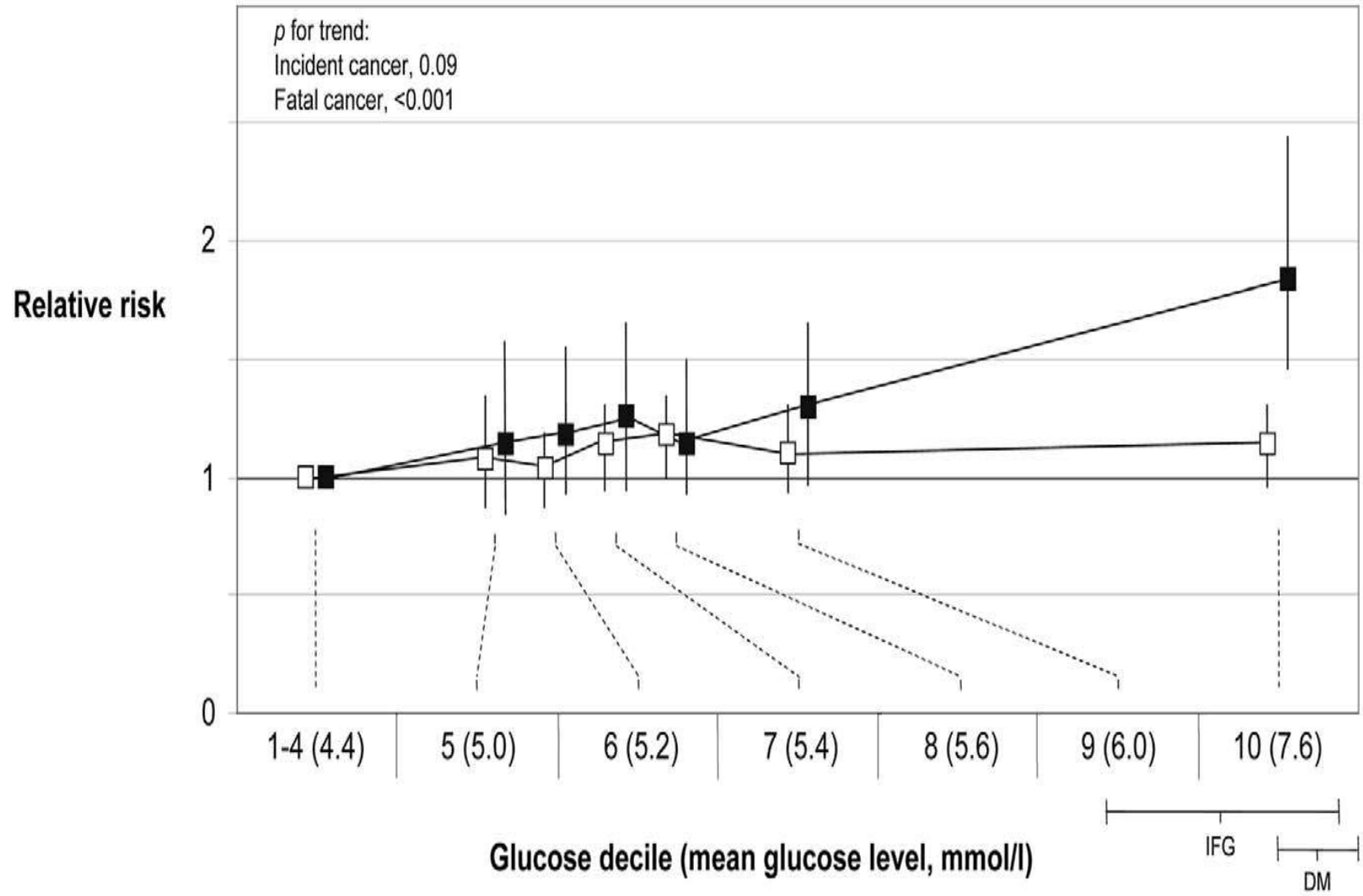
Hiperglisemi ve kanser tiplerinin ilişkisi

Vasterbotten Intervention Project of Northern Sweden

	Açlık glukozu RR (%95 GA)	P_{trend}	OGTT-2st glukoz RR (%95 GA)	P_{trend}
Pankreas	2.49 (1.23-5.45)	0.006	0.91 (0.47-1.78)	0.910
Endometrium	1.86 (1.09-3.31)	0.454	1.82 (1.07-3.23)	0.028
Meme	1.06 (0.82-1.37)	0.019	1.20 (0.93-1.55)	0.069
Üriner sistem	1.69 (0.95-3.16)	0.049	1.18 (0.65-2.17)	0.781
Malign melanom	2.16 (1.14-4.35)	0.013	1.65 (0.89-3.17)	0.086
Non-Hodgkin lenfoma	1.89 (4.09-1.62)	0.786	2.53 (1.16-6.11)	0.081
Prostat	0.96 (0.74-1.26)	0.713	0.79 (0.61-1.02)	0.074

Stattin P, et al. Diabetes Care 2007;30:561-67

Kan Şekeri ve Kanser İlişkisi



Incident cancer	1 (referent)	1.07 (0.87-1.33)	1.03 (0.87-1.21)	1.14 (0.93-1.33)	1.18 (1.00-1.37)	1.10 (0.93-1.33)	1.14 (0.97-1.33)
Fatal cancer	1 (referent)	1.14 (0.81-1.59)	1.18 (0.90-1.55)	1.25 (0.93-1.69)	1.14 (0.90-1.50)	1.29 (0.97-1.69)	1.84 (1.46-2.40)

Stocks et al. www.plosmedicine.org. 2009

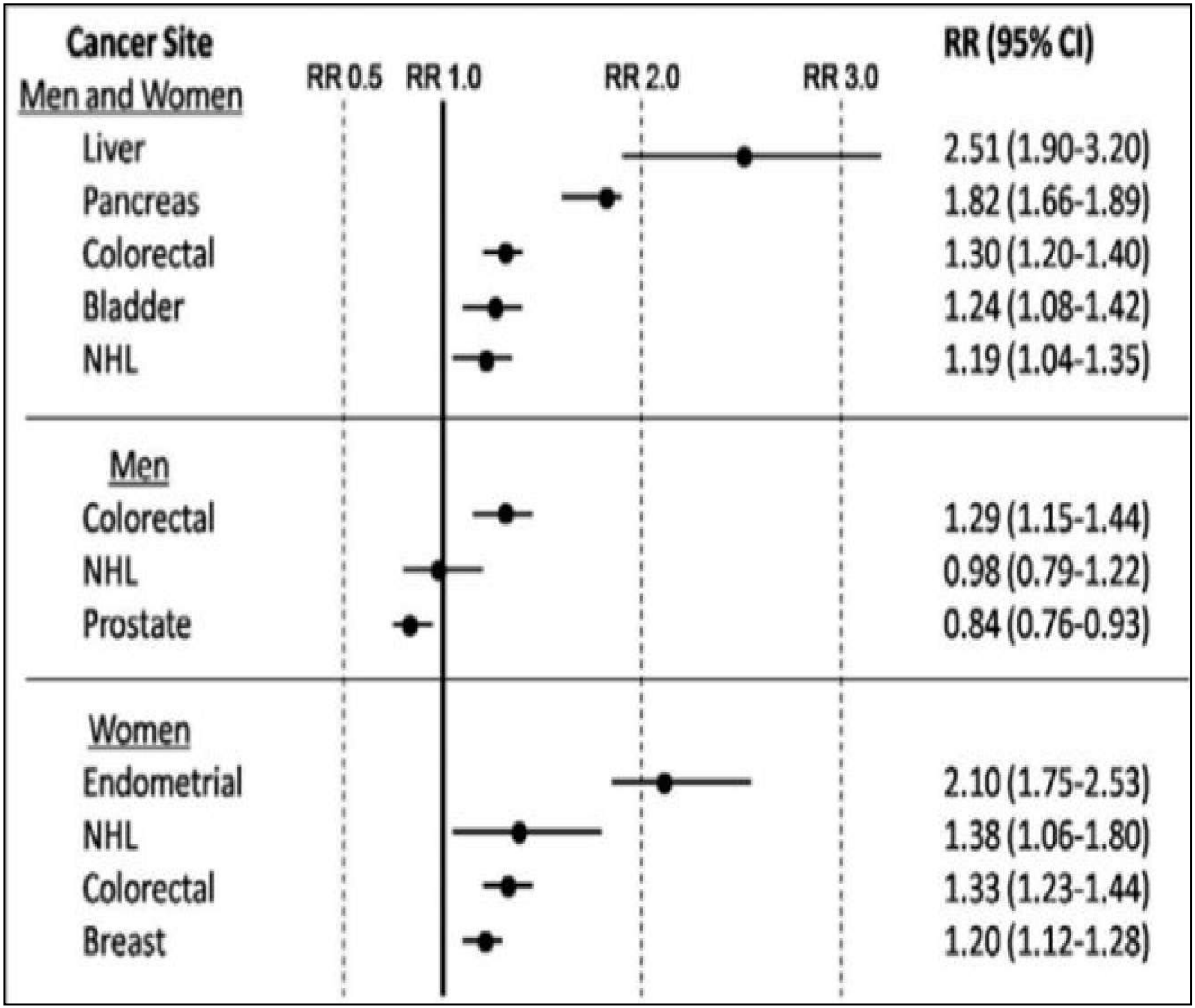
Diyabet ve kolorektal kanser

- İsveçli erkek kohortunda diyabet ve kanser insidansı
- 1997-2004 arası takip edilen 47-79 yaş grubunda 48.550 erkek

	DİYABET ÖYKÜSÜ		***P değeri***
	YOK	**VAR**	
Kolorektal Ca			
Yaşa göre ayarlanmış RR (%95 GA)	1.00	1.45 (1.11–1.89)	0.006
Multivaryant RR (%95 GA)	1.00	1.49 (1.14–1.96)	0.004
Kolon Ca			
Yaşa göre ayarlanmış RR (%95 GA)	1.00	1.46 (0.98–2.17)	0.06
Multivaryant RR (%95 GA)	1.00	1.53 (1.02–2.29)	0.04
Rektal Ca			
Yaşa göre ayarlanmış RR (%95 GA)	1.00	1.76 (1.17–2.65)	0.007
Multivaryant RR (%95 GA)	1.00	1.79 (1.18–2.73)	0.007

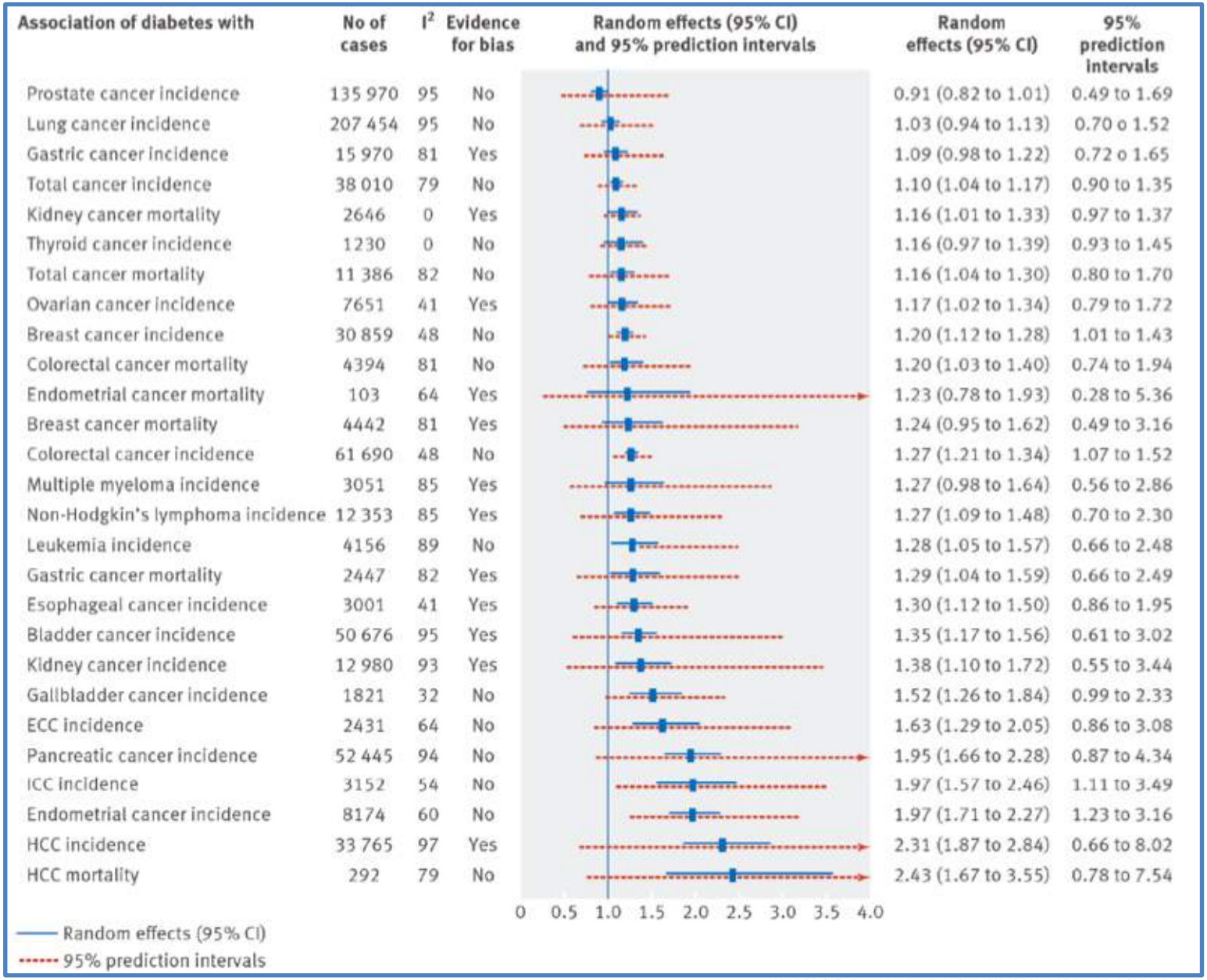
Larsson SC, et al. Diabetes Care 2005;28:1805-07

Tip 2 Diyabetli Hastalarda Kanser Riski



Calaghan EJ, et al. Endocrine Pract 2010;16:864

Tip 2 diyabette kanser insidansi veya mortalitesi: 27 metaanalize ilişkin verilerin özeti



Association of diabetes with	No of cases	I^2	Evidence for bias	Random effects (95% CI) and 95% prediction intervals	Random effects (95% CI)	95% prediction intervals
Prostate cancer incidence	135 970	95	No		0.91 (0.82 to 1.01)	0.49 to 1.69
Lung cancer incidence	207 454	95	No		1.03 (0.94 to 1.13)	0.70 o 1.52
Gastric cancer incidence	15 970	81	Yes		1.09 (0.98 to 1.22)	0.72 o 1.65
Total cancer incidence	38 010	79	No		1.10 (1.04 to 1.17)	0.90 to 1.35
Kidney cancer mortality	2646	0	Yes		1.16 (1.01 to 1.33)	0.97 to 1.37
Thyroid cancer incidence	1230	0	No		1.16 (0.97 to 1.39)	0.93 to 1.45
Total cancer mortality	11 386	82	No		1.16 (1.04 to 1.30)	0.80 to 1.70
Ovarian cancer incidence	7651	41	Yes		1.17 (1.02 to 1.34)	0.79 to 1.72
Breast cancer incidence	30 859	48	No		1.20 (1.12 to 1.28)	1.01 to 1.43
Colorectal cancer mortality	4394	81	No		1.20 (1.03 to 1.40)	0.74 to 1.94
Endometrial cancer mortality	103	64	Yes		1.23 (0.78 to 1.93)	0.28 to 5.36
Breast cancer mortality	4442	81	Yes		1.24 (0.95 to 1.62)	0.49 to 3.16
Colorectal cancer incidence	61 690	48	No		1.27 (1.21 to 1.34)	1.07 to 1.52
Multiple myeloma incidence	3051	85	Yes		1.27 (0.98 to 1.64)	0.56 to 2.86
Non-Hodgkin's lymphoma incidence	12 353	85	Yes		1.27 (1.09 to 1.48)	0.70 to 2.30
Leukemia incidence	4156	89	No		1.28 (1.05 to 1.57)	0.66 to 2.48
Gastric cancer mortality	2447	82	Yes		1.29 (1.04 to 1.59)	0.66 to 2.49
Esophageal cancer incidence	3001	41	Yes		1.30 (1.12 to 1.50)	0.86 to 1.95
Bladder cancer incidence	50 676	95	Yes		1.35 (1.17 to 1.56)	0.61 to 3.02
Kidney cancer incidence	12 980	93	Yes		1.38 (1.10 to 1.72)	0.55 to 3.44
Gallbladder cancer incidence	1821	32	No		1.52 (1.26 to 1.84)	0.99 to 2.33
ECC incidence	2431	64	No		1.63 (1.29 to 2.05)	0.86 to 3.08
Pancreatic cancer incidence	52 445	94	No		1.95 (1.66 to 2.28)	0.87 to 4.34
ICC incidence	3152	54	No		1.97 (1.57 to 2.46)	1.11 to 3.49
Endometrial cancer incidence	8174	60	No		1.97 (1.71 to 2.27)	1.23 to 3.16
HCC incidence	33 765	97	Yes		2.31 (1.87 to 2.84)	0.66 to 8.02
HCC mortality	292	79	No		2.43 (1.67 to 3.55)	0.78 to 7.54

BMJ 2014;350:g7607 doi: 10.1136/bmj.g7607 (

T2DM'li Hastalarda Kanser Risk Faktörleri

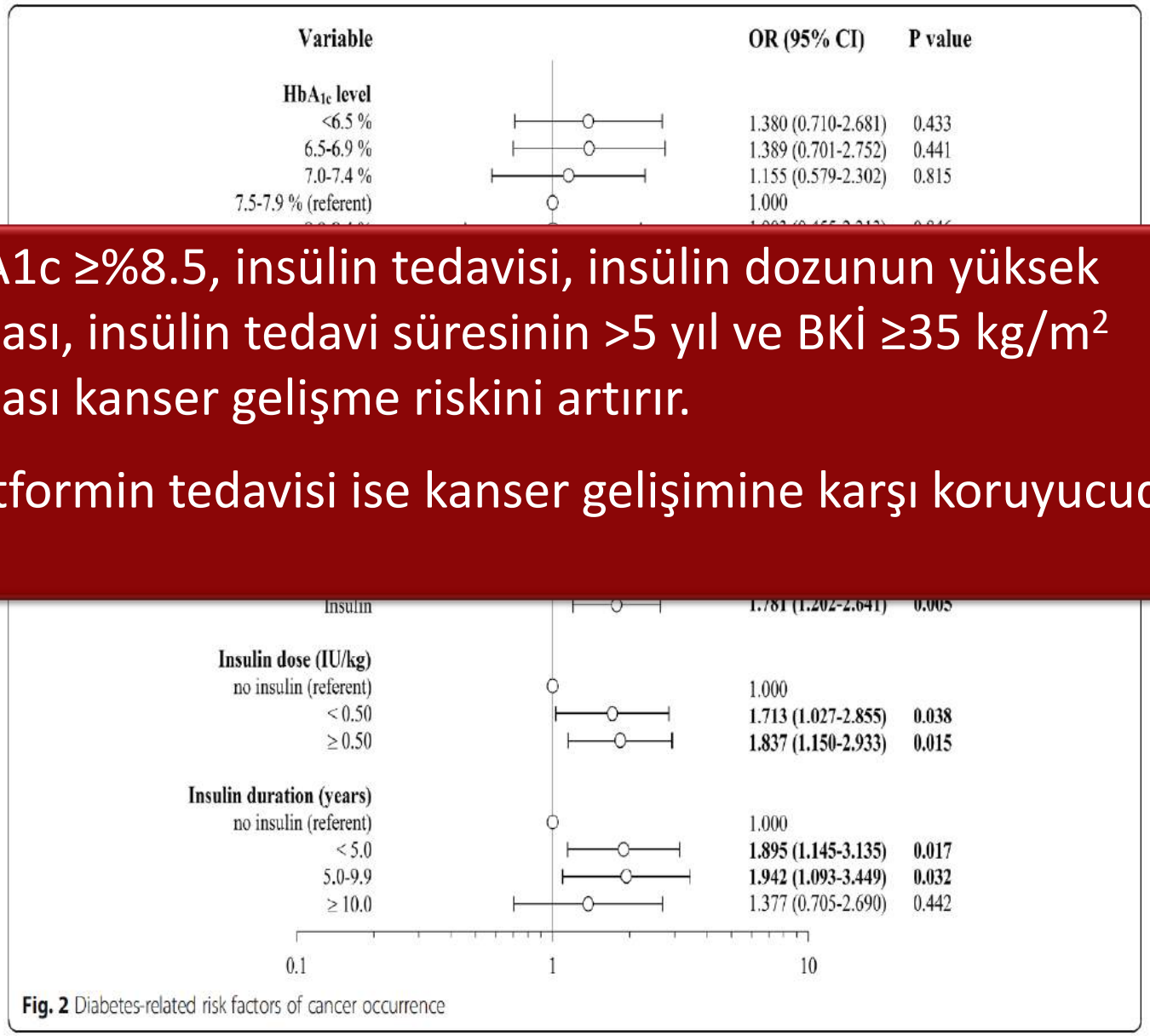


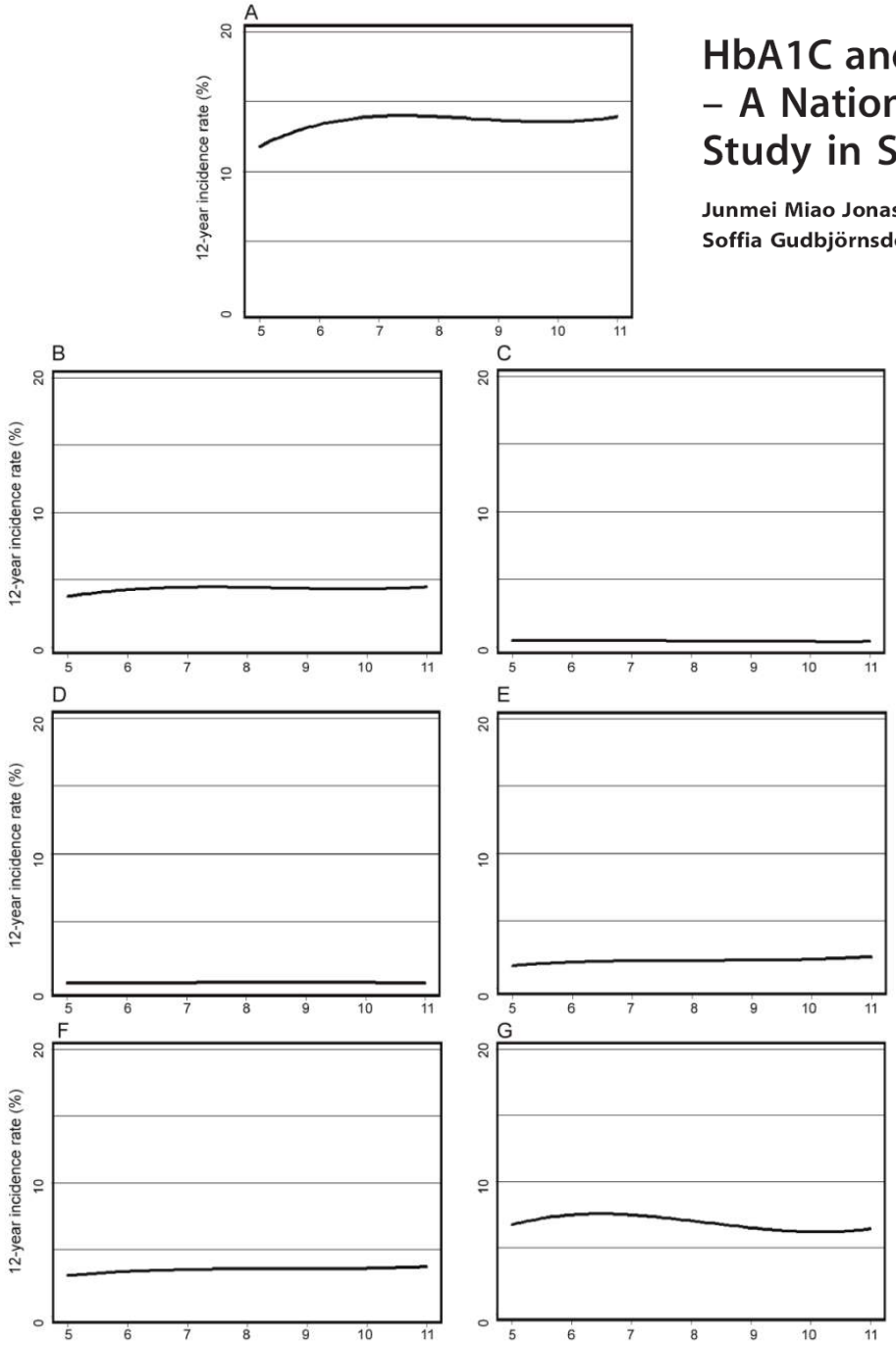
Fig. 2 Diabetes-related risk factors of cancer occurrence

- HbA1c ≥%8.5, insülin tedavisi, insülin dozunun yüksek olması, insülin tedavi süresinin >5 yıl ve BKİ ≥35 kg/m^2 olması kanser gelişme riskini artırır.
- Metformin tedavisi ise kanser gelişimine karşı koruyucudur.

Dąbrowski M, et al. BMC Cancer (2016) 16:785

HbA1C and Cancer Risk in Patients with Type 2 Diabetes – A Nationwide Population-Based Prospective Cohort Study in Sweden

Junmei Miao Jonasson[1,2*], Jan Cederholm[3], Björn Eliasson[4], Björn Zethelius[5,6], Katarina Eeg-Olofsson[4], Soffia Gudbjörnsdottir[1,4]



A. 12-year incidence of all cancer;
B. 12-year incidence of gastrointestinal cancer;
C. 12-year incidence of cancer in kidney and urinary organs;
D. 12-year incidence of cancer in respiratory organs;
E. 12-year incidence of cancer in female genital organs; F. 12-year incidence of breast cancer;
G. 12-year incidence of prostate cancer

PLoS One 2012; 7: e38784.

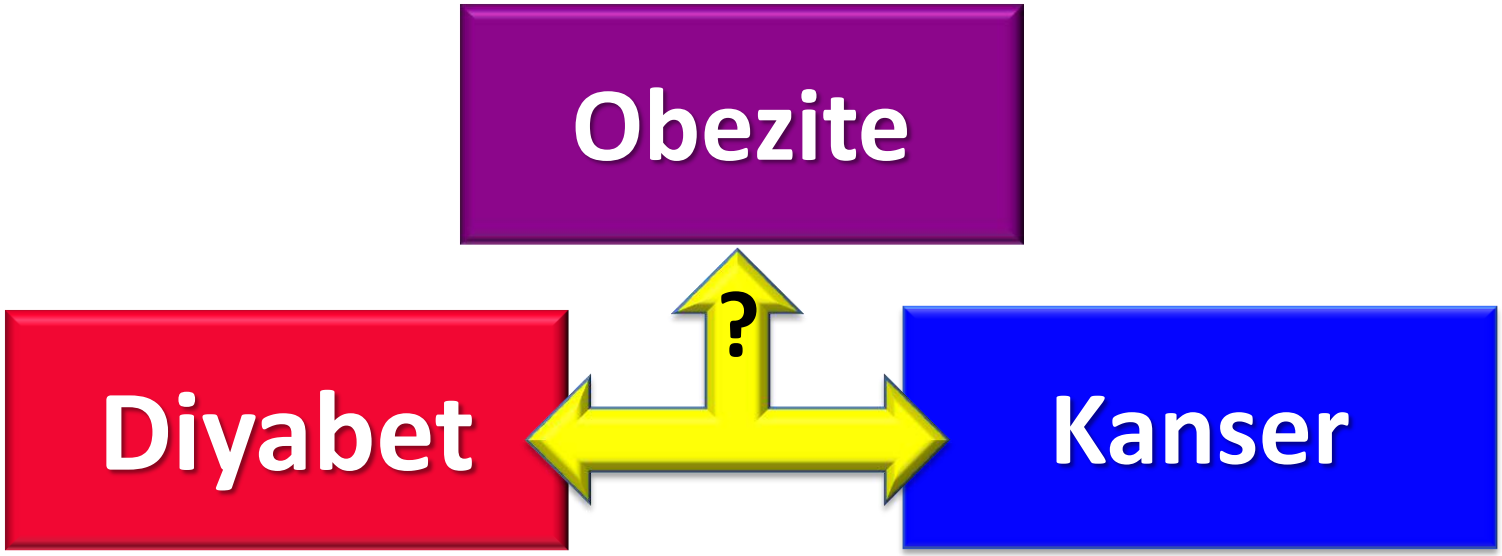

Obezite
?
Diyabet
Kanser

Table 1
Meta-analyses Linking Increased BMI (≥25 kg/m^2) With Cancer Risk

Study group	Cancer evaluated	Risk	95% CI
Druesne-Pecollo et al 2012 (7)	Endometrial (second primary)	RR 1.46[a]	1.17-1.83
	Breast (second primary)	RR 1.14[a]	1.07-1.21
	Breast (contralateral)	RR 1.12[a]	1.06-1.20
Crosbie et al 2010 (6)	Endometrial	RR 1.60[a]	1.52-1.68
Renehan et al 2008 (men) (9)	Esophageal (adenocarcinoma)	RR 1.52[a]	1.33-1.74
	Thyroid	RR 1.33[a]	1.04-1.70
	Colon	RR 1.24[a]	1.20-1.28
	Renal	RR 1.24[a]	1.15-1.34
	Malignant melanoma	RR 1.17[a]	1.05-1.30
	Multiple myeloma	RR 1.11[a]	1.05-1.18
	Rectal	RR 1.09[a]	1.06-1.12
	Leukemia	RR 1.08[a]	1.02-1.14
	Non-Hodgkin lymphoma	RR 1.06[a]	1.03-1.09
	Lung	RR 0.76[a]	0.70-0.83
	Esophageal (squamous)	RR 0.71[a]	0.60-0.85
Renehan et al 2008 (women) (9)	Endometrial	RR 1.59[a]	1.50-1.68
	Gallbladder	RR 1.59[a]	1.02-2.47
	Esophageal (adenocarcinoma)	RR 1.51[a]	1.31-1.74
	Renal	RR 1.34[a]	1.25-1.43
	Leukemia	RR 1.17[a]	1.04-1.32
	Thyroid	RR 1.14[a]	1.06-1.23
	Breast (postmenopausal)	RR 1.12[a]	1.08-1.16
	Pancreatic	RR 1.12[a]	1.02-1.22
	Multiple myeloma	RR 1.11[a]	1.07-1.15
	Colon	RR 1.09[a]	1.05-1.13
	Breast (premenopausal)	RR 0.92[a]	0.88-0.97
	Lung	RR 0.80[a]	0.66-0.97
Schouten et al 2008 (10)	Ovarian (premenopausal)	RR 1.72[b]	1.02-2.89
	Ovarian (Postmenopausal)	RR 1.07[b]	0.87-1.33
Olsen et al 2007 (8)	Ovarian	RR 1.30[c]	1.12-1.50

Abbreviations: BMI = body mass index; CI = confidence interval; RR = relative risk.
[a] Risk values per 5-kg/m^2 increase in BMI.
[b] Multivariate risk, obese (BMI≥30 kg/m^2) versus nonobese (BMI 18.5-23 kg/m^2) patients.
[c] Pooled risk, obese (BMI≥30 kg/m^2) versus nonobese (BMI 18.5-24.9 kg/m^2) patients.

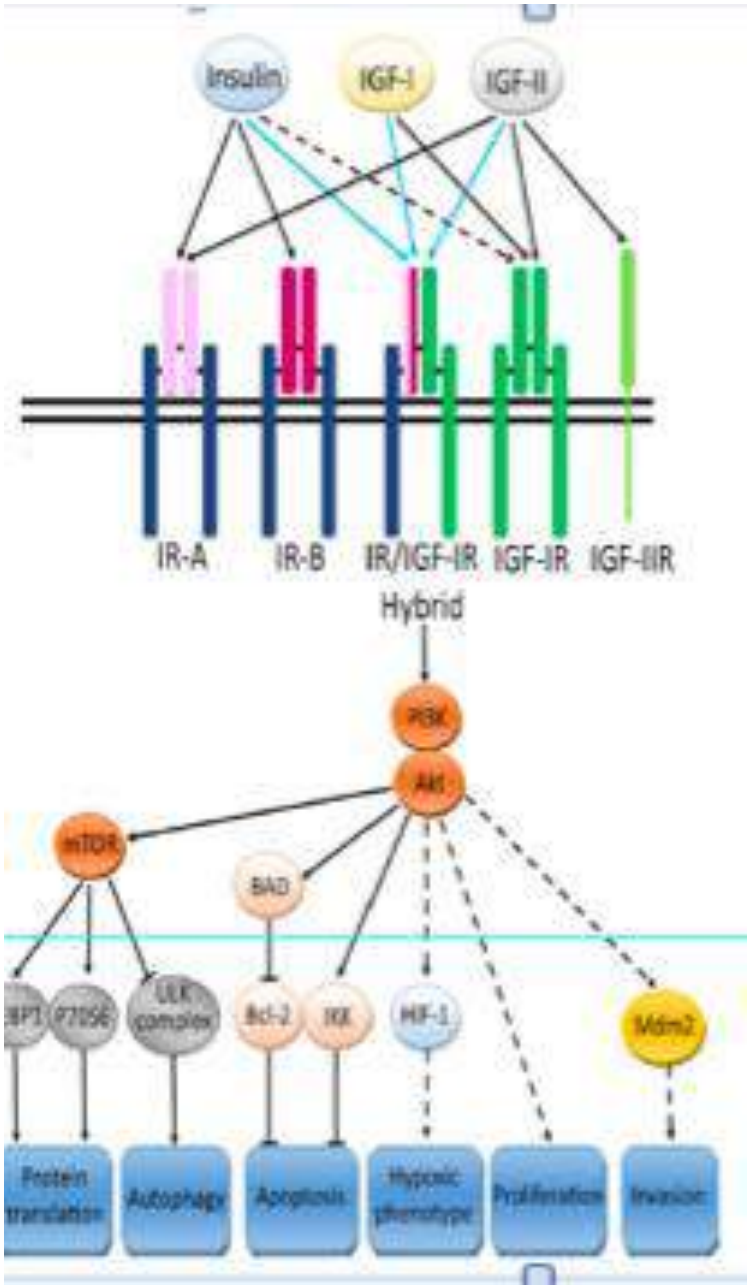
Diabetes and Cancer, *Endocr Pract.* 2013;19(No. 4)

Diyabet ve kanser ilişkisinde olası mekanizmalar

- İnsulin direnci ve IGF sinyal yolağı aktivasyonu
- Obezite ve inflamasyon
- Direkt metabolik etkiler ve metabolik simbiyozis
- ER stres
- Otofaji

F. Hua et al.Cancer Letters 374 (2016) 54–61

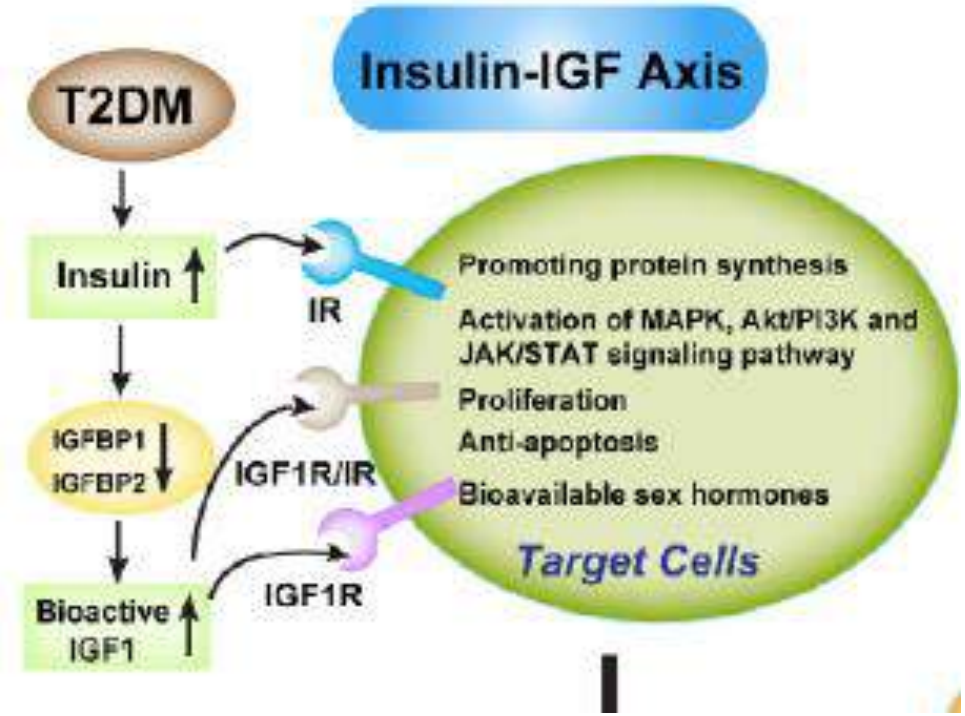
- IR ile IGF-IR homolog ve benzer sinyal yollarını paylaşır.
- İnsülin, IGF-I reseptörüne IR-A ve IR-B'den daha fazla bağlanma kabiliyetine sahip ancak daha düşük bir afinitede
- IGF-I IGF-I R ve IR / IGF-IR hibrid R bağlama yeteneğine sahip
- IR-B'nin aktivasyonu metabolik etkilere IR-A ve IR / IGF-IR HR aktivasyonu, mitojenik etkilere neden olur.



Shafiei-Irannejad et al. Chem Biol Drug Des. 2017

İnsülin direnci-kanser ilişkisi

- Kanser hücresinde IGF-1/IR hibrid res➔büyüme sinyallerine duyarlılık
- Karaciğer IGFBP sentezinde🡻
  - ➔IGF-1 biyoyararlanımında artış
  - ➔Hücre proliferasyonu
  - ➔Anjiyogenez-lenfanjiyogenez
  - ➔Apoptoz inhibisyonu
- SHBG🡹
  - Östrojen biyoyararlanımında artış
  - IGF-1 ile sinerjistik etki: hücre proliferasyonunda uyarılma
  - Östrojene duyarlı tm artışı: postmenopozal endometrium, meme ca



Becker et al. Arch Physiol Biochem, 115(2):86-96.
Xue et al. Amer J Clin Nutr, 86(3):s823-35
Hjartaker et al. Adv Exp Med Biol, 630:72-93..

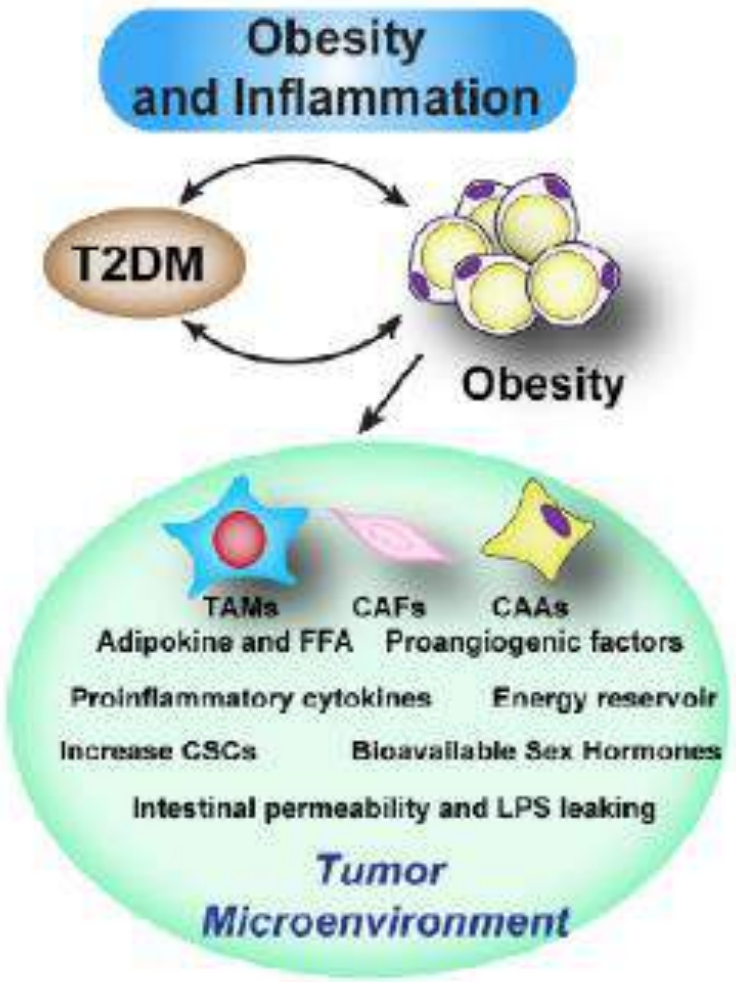
Plazma insulin, C-Peptid ve IGF-1 artışı ile kanser ilişkisi

Study group	Cancer evaluated	Risk	95% CI
Insulin			
Hirose et al 2003 (41)	Postmenopausal breast cancer	OR 4.48[b]	1.07-18.7
Goodwin et al 2002 (40)	Breast cancer (distant recurrence)	HR 2.0	1.20-3.30
	Breast cancer death	HR 3.1	1.70-5.70
Mink et al 2002 (42)	Breast cancer	RR 1.01[c]	0.55-1.86
Del Giudice et al 1998 (39)	Premenopausal breast cancer	OR 2.83[d]	1.22-6.58
C-Peptide			
Wolpin et al 2009 (47)	Nonmetastatic colorectal death	HR 1.87[e]	1.04-3.36
Pisani et al 2008 (46)	Colorectal	RR 1.35	1.13-1.61
	Breast	RR 1.26	1.06-1.48
	Pancreatic	RR 1.70	1.10-2.63
	Bladder	RR 1.22	1.01-1.47
Ma et al 2004 (44)	Colorectal	RR 2.7[f]	1.20-6.20
IGF-1			
Duggan et al 2013 (43)	Breast cancer (all-cause mortality)	HR 3.10[g]	1.21-7.93
Ma et al 1999 (45)	Colorectal	RR 2.51	1.15-5.46

Diabetes and Cancer, Endocr Pract. 2013;19(No. 4)

Obezite ve kanser ilişkisi

- Tümör stroma hücreleri: Kanser ile ilişkili fibroblast, makrofaj ve adipositler
- Tümör çevresindeki adipoz doku artışı
  - ➔Hipoksi
  - ➔Makrofaj, T hücre ve NK infiltrasyonu
  - ➔FFA, TNFα, IL-6, IL-8, IL-18↑
  - ➔Leptin ↑
    - ➔VEGF ve proanjiyojenik faktör artışı
  - ➔Tümörde progresyon
  - ➔Tedaviye rezistans



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Obezitenin diğer etkileri

- İntestinal permeabilite artışı ve LPS kaçışı➔Düşük dereceli enflamasyon ve karsinojenezis: Kolon tm
- Yağ alımında artış ➔İB Gr +↑ deoksikolik asit ↑
  - DNA hasarı
  - Karaciğerde inflamasyon ve HCC riski
- Aromataz aktivitesinde artış ➔Androjenik prekürsörlerden östradiole dönüşüm

Meme:

- Mitojenik ve mutajenik etkiler
- DNA hasarı
- Genetik instabilite ve normal meme hücresi ile meme ca hücresinde mutasyonla

Endometrium

- Hücre proliferasyonu
- Antiapoptotik etkiler
- Lokal IGF-1 sentezi

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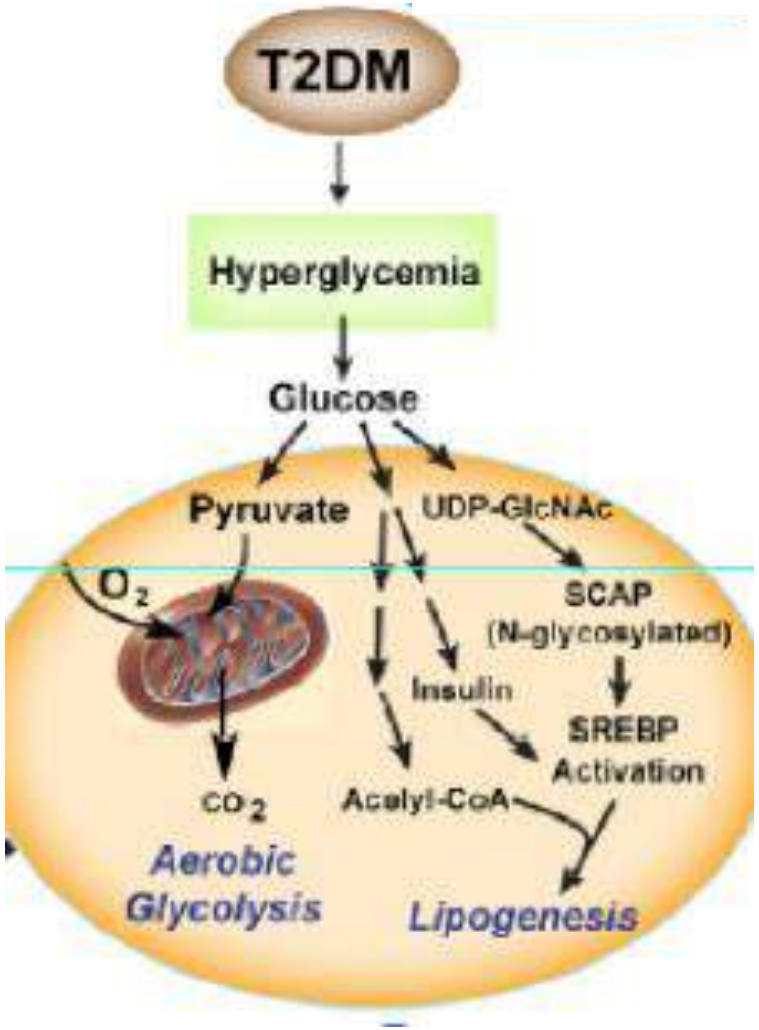
Metabolik simbiozis ve kanser

- Kanser hücresi glukoza bağımlıdır!
- Stromal hücreler aerobik glikoliz ile ca hücresine laktat ve piruvat, lipoliz ile FFA sağlar.
- Hiperglisemi
  - Yakıt fazlalığı
  - NF-κB aktivasyonu
  - İnflamasyon



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İnflamasyon

- Pro-inflamatuar sitokin↑ IL-6, TNF-α
- Serbest radikal artışı
- ➔DNA hasarı
- ➔İnsülin direnci
- ➔Kanser gelişimi ve tümör büyüklüğünde artış

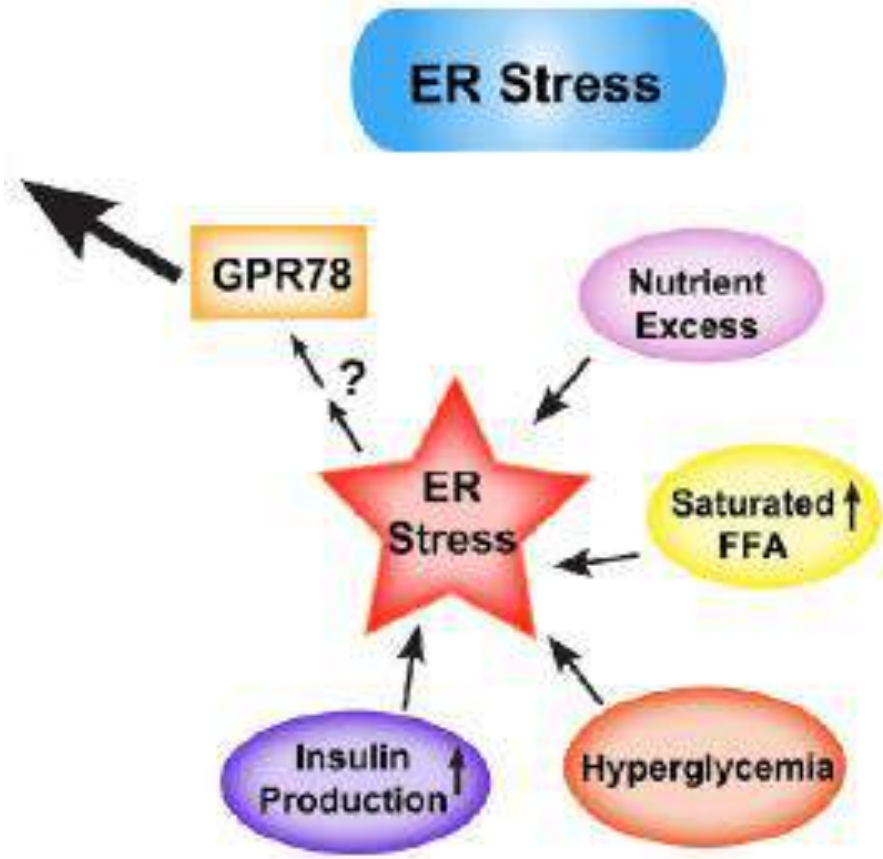
Godslan et al. Clin Sci (Lond), 118(5):315-32.
Vigneri et al. Endocr Relat Cancer, 16(4):1103-23.

ER stres ve kanser

- β-hücresinde ERS: Aşırı nutrient akımı, ↑protein sentezi + matürasyon defekti→beta hücresi ölümü
- Ca hücresinde ERS: Düşük pO2 ve pH→ UPR ve ROS ↑
- Glucose-regulated protein 78↑: ER strese adaptif cevap , leptin ve glukoz artışı ile tetiklenir

  →Tümör reküransı

  →Tedaviye direnç



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Otofaji ve kanser

- Diyabet ve kanser patolojisinde rol oynayan degradasyon sistemleri
  - Proteazom: Kısa yaşam süreli proteinler
  - Lizozom: Uzun yaşam süreli proteinler, hasarlı organeller
  - Tm hücresinde defektif otofaji
    - Beclin1 delesyonu: Meme, over, prostat ca
      - PI3K aktivasyonunda süpresyon defekti ➔proliferasyon

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Kolorektal kanser ile ilişkili genlere diyabetin etkisi

Table 1: Genetics of colorectal cancer and potential impact of DM on colorectal cancer-related genes

Colorectal cancer	Mutation	Inheritance	Impact of DM on gene expression *	Reference
Familial adenomatous polyposis	Inactivating germline mutation in adenomatous polyposis coli (*APC*)	Autosomal dominant	Increased *APC*	[283,284]
MUTYH-associated polyposis	Inactivating germline mutation in *MUTYH*	Autosomal recessive	Unchanged *MUTYH*	[283,284]
Peutz-Jeghers syndrome	Inactivating germline mutation in serine threonine kinase 11 (*STK11*)	Autosomal dominant	Increased *STK11*	[285]
Hereditary non-polyposis colorectal cancer (Lynch syndrome)	Inactivating germline mutation in *MLH1*, *MSH2*, *MSH6*, or *PMS2*	Autosomal dominant	Unchanged *MLH1*, *PMS2* Increased *MSH2*, *MSH6*	[286]
Chromosomal instability (frequent)	Acquired accumulation of numerical (aneuploidy) or structural chromosomal abnormalities and mutations in specific oncogenes and tumor suppressor genes (e.g. *APC*, *PIK3CA*, *SMAD4*, *KRAS*, *TP53*, *BRAF*)		Unchanged *PIK3CA*, *SMAD4*, *BRAF* Increased *KRAS*, *TP53*	[287–289]

* Kidney gene expression in human diabetic kidney disease transcriptomics (http://www.nephromine.org)

Gonzalez et al, Oncotarget, 2017, Vol. 8, 18456-18485

AMERICAN INSTITUTE for CANCER RESEARCH

Type 2 Diabetes and the Link to Certain Cancers: Risk and Possible Mechanisms

Cancer Site	Risk Ratio* (95% CI) in meta-analysis of cohort studies	Potential mechanisms
Liver Cancer	2.51 (1.9-3.2) 7 cohort studies (El-Serag H, 2006)	• Insulin resistance leads to non-alcoholic fatty liver disease, which allows damage from free radicals and inflammatory cytokines. This may lead to cirrhosis and then cancer. • Possibly some effect of more hepatitis infections.
Pancreatic Cancer	1.73 (1.59-1.88) 19 cohort studies (Huxley R, 2005)	• Obesity • Elevated insulin • Oxidative stress from hyperglycemia • Association may reflect diabetes not only as risk but also as an early consequence of pancreatic cancer.
Endometrial Cancer	1.62 (1.21–2.16) 3 cohort studies (Friberg E, 2007)	• High levels of insulin and free IGF-1 • Increased bioavailable estrogen
Bladder	1.43 (1.18–1.74) 3 cohort studies (Larsson S, 2006)	• Hyperinsulinemia and increased IGF-1 • Possibly more urinary tract infections with diabetes
Non-Hodgkin Lymphoma	1.41 (1.07-1.88) 5 cohort studies (Mitri J, 2008)	• Abnormal immune function in diabetes
Colorectal Cancer	1.29 (1.16–1.43) 9 cohort studies (Larsson S, 2005) 1.23 (1.17-1.30) 15 cohort studies (Huxley R, 2009)	• Hyperinsulinemia • Inflammation • Slower bowel transit time • Elevated fecal bile acid concentrations
Breast Cancer (postmenopausal probably more affected than pre-menopausal)	1.20 (1.11–1.30) 15 cohort studies (Larsson S, 2007)	• High levels of insulin and IGF-1 • Increased bioavailable estradiol and testosterone resulting from inhibited sex-hormone binding globulin (SHBG) production