

KING'S College LONDON

A role for lipids and statins in breast cancer risk and prevention?

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Lipid metabolism and cancer

An estimated 17,294 excess cancer cases occurred in 2010 due to overweight and obesity (5.5% of all cancers).

www.dietandcancerreport.org

RECOMMENDATION 1

BODY FATNESS

Be as lean as possible within the normal range[1] of body weight

PUBLIC HEALTH GOALS

Median adult body mass index (BMI) to be between 21 and 23, depending on the normal range for different populations[2]

The proportion of the population that is overweight or obese to be no more than the current level, or preferably lower, in 10 years

PERSONAL RECOMMENDATIONS

Ensure that body weight through childhood and adolescent growth projects[3] towards the lower end of the normal BMI range at age 21

Maintain body weight within the normal range from age 21

Avoid weight gain and increases in waist circumference throughout adulthood

AMORIS

- Swedish Apolipoprotein MOrtality RISk study = AMORIS
- Blood analyses from general health check-ups between 1985 and 1996 in Stockholm area
- Linkage to National Registries using Personal Identification Numbers >500 different biomarkers

Database	Coverage	N	Outcome	Demography	Lifestyle	Comorbidity
Clinical Cancer Quality Register						
Breast	1985-2011	15,881	•			
Prostate	1996-2012	17,141	•			
Colorectal	1991-2012	6,135	•			
Swedish Cancer Register	1958-2011	148,364	•			
Cause of Death Register	1961-2011	153,800	•			•
National Patient Register	1964/87-2011	Outpatient: 683,747 – Inpatient: 696,825	•			•
Total Population Register	1968-2012	800,587	•	•		
Census Data	1907-1990	783,922		•		
LISA database	1992-2010	799,647		•		
Medical Birth Register	1973-2011	204,449			•	
Multigeneration Register	1932-2011	812,073			•	
National Diabetes Register	1996-2011	58,985			•	•
Prescribed Drug Register	2005-2012	681,299			•	•
Karolinska Institutet (5 Research Cohorts)	1963-1990	29,000		•	•	•
AMORIS cohort (Biomarker measurements)	1985-1996	**812, 073**				

Serum Lipids and Breast Cancer in AMORIS

- 234,494 women with baseline measurements of triglycerides, total cholesterol, and glucose
- A weak protective association was found between levels of triglycerides and risk of breast cancer.

	Breast Cancer *N = 6,105*	
Triglycerides (mmol/L)	**HR**	**(95%CI)**
< 0.70	1.00	(ref)
0.70-0.90	1.01	(0.94-1.09)
0.90-1.30	0.93	(0.86-1.00)
≥ 1.30	0.91	(0.84-0.99)
Ptrend	0.01	

Melvin et al. CEBP 2012

Serum Lipids and Breast Cancer Severity in AMORIS

- 1,824 women diagnosed with breast cancer
- Breast cancer severity was split into categories (good, moderate, and poor prognosis) based on ER status, TNM stage, and age at diagnosis.
- Serum glucose (</≥ 5.60 mmol/L) and BC severity (proportional OR: 1.25 (95%CI: 0.92-1.70)
- ApoB/A-1 ratio (</≥ 1) and BC severity: 1.31 (95%CI: 0.97-1.76)

→ Only modest positive association between serum levels of glucose, apoB/ApoA-1 and breast cancer severity.

→ Suggesting that these factors are not the main players in linking obesity and breast cancer aggressiveness.

Statins and cancer

- Cholesterol is fundamental for cell proliferation → influence the progression of cancer
- May impair the growth of multiple cancer types
- Suggested underlying mechanisms:
  - lowering cholesterol levels
  - normalising serum triglyceride levels
  - intracellular signalling pathways
  - anti-inflammatory effects
- Observational studies show inconsistent results
- No trial data are available yet

Statins and breast cancer

First Author	Year	Association studied	Population/Study Type	Conclusion
Undela	2012	Breast cancer	Meta-analysis of observational studies	Our findings do not support the hypothesis that statins have a protective effect against breast cancer
Ahern	2011	Breast cancer recurrence	Prospective cohort	Simvastin was associated with a reduced risk of breast cancer
Chae	2011	Breast cancer recurrence	Retrospective hospital-based	The use of statins was associated with a reduced risk of breast cancer recurrences
Woditschka	2010	Breast cancer	Retrospective cohort	These results do not support an association of lipophilic statin use with the risk of breast cancer.
Eaton	2009	Breast cancer	Hospital-based case-control study	This observational study found an increased risk of breast cancer related to duration of statin use among postmenopausal women
Kwan	2008	Breast cancer recurrence	Prospective cohort	Inverse association between post-diagnosis, lipophilic statin use and risk of breast cancer recurrence.
Pocobelli	2008	Breast cancer risk	Prospective case-control	Use of statins overall was not associated with breast cancer risk
Cauley	2006	Breast cancer risk	Prospective cohort	Statin use was not associated with invasive breast cancer incidence.

So what is the association?

- Given the inconsistent findings from observational data to date and the lack of results from RCTs, it is of interest to apply newer epidemiological methods in an attempt to find out about the potential protective effects of statins in terms of cancer management → Causal Inference

Causal Inference

- Treat observational data as if it were RCT data
- Predict probability of treatment arm based on potential confounders
- Every patient gets a weight for being in a treatment arm

Comment

BJUI
BJU International

An investigation into the relationship between statins and cancer using population-based data

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Case study: BCBaSe Sweden

A total of 272 breast cancer-specific death cases were matched to 1,360 controls.

Table 6.3 *Baseline characteristics for all cases with breast cancer specific death and their matched controls*

	Cases (n = 272) (%)	Controls (n = 1360) (%)	*P* value*
Age at diagnosis, y			
Mean (SD)	71.12 (14.09)	64.27 (14.84)	<0.0001
Socioeconomic status			
White collar	55 (20.22)	318 (23.38)	<0.0001
Blue collar	67 (24.63)	514 (37.79)	
Not gainfully employed/missing	150 (55.15)	528 (38.82)	
Education			
Lower secondary	130 (47.79)	396 (29.12)	
Secondary	74 (27.21)	482 (35.44)	<0.0001
Higher education	50 (18.38)	421 (30.96)	
Unknown/Missing	18 (6.62)	61 (4.49)	
Mean follow-up time, y			
Mean (SD)	0.97 (0.75)	3.48 (1.09)	<0.0001
Menopausal status at diagnosis			
Pre-menopausal	25 (9.19)	272 (20.00)	0.0001
Post-menopausal	236 (86.76)	1035 (76.10)	
Missing	11 (4.04)	53 (3.90)	
Age at first birth			
<20	88 (32.35)	394 (28.97)	0.14
20-29	144 (52.94)	722 (53.09)	
≥30	40 (14.71)	244 (17.94)	
Parity			
0	51 (18.75)	208 (15.29)	
1	62 (22.79)	265 (19.49)	0.18
2	85 (31.25)	532 (39.12)	
≥3	74 (27.21)	355 (26.10)	

Findings

Table 6.4. *Hazard ratios and 95% confidence intervals for statin use on the risk of breast cancer specific death.*

Model	HR	95% Confidence Interval
Preliminary*	0.56	0.38-0.84
Baseline adjusted^	0.87	0.77-0.99

*Adjusted for age at baseline as a continuous variable

^ Adjusted for baseline characteristics (region, education, civil status, initial treatment, stage of disease, mode of detection, year of diagnosis, country of birth, CCI) with time-dependent confounders entered as time-updated covariates

Preliminary model ~ unadjusted Cox proportional hazards model

Baseline adjusted → Erroneous!

* Weights vary from 0.003 to 8.8e+27
* Positivity assumption

Interpretation

- Baseline model: statins less likely to be prescribed among those with more severe cancer? Hypercholesterolemia not a major concern.
- Validity of causal inference model:
  - Large weights
  - Positivity assumption

What next?

- Clear distinction between statins before and after cancer diagnosis
- Need to take into account disease severity
- Data on serum cholesterol levels needed

→ **Even advanced causal inference methods are unable to make clear inferences**

→ **No published studies present information on serum cholesterol levels and disease severity in a single setting**

→ **Need for a well-defined RCT**

Thank you

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BCBaSe and PCBaSE Sweden