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Fluvastatin and the Breast Cancer Risk: A Meta-analysis of Observational Studies

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ABSTRACT

Multiple studies have investigated the associations between fluvatatin and the risk of breast cancer (BC), but their results were conflicting. A meta-analysis of observational studies published regarding this subject was conducted in the present study. It aims to estimate the associations between fluvastatin use and the risk of BC. Pubmed and chinese national knowledge infrastructure (CNKI) database was searched up to January, 2015 to identify eligible observational studies, and the Newcastle-Ottawa Scale (NOS) was used to assess quality of the studies. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated (fixed effect model: Mantel-Haenszel). Heterogeneities were evaluated before the calculation. A sensitivity analysis was also conducted. In total, four studies contributed to the analysis. Overall, fluvastatin use negatively correlated with BC risk (RR = 0.74, 95 % CI = 0.58, 0.95). In conclusion, fluvastatin use may reduce the risk of BC, but more research is needed to confirm this finding.

Key words: Fluvastatin, Breast cancer, Meta-analysis
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INTRODUCTION

Statins, also 3-hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, are widely used because of its effect in reducing atherosclerotic cardiovascular disease (CVD) events via depressing cellular cholesterol synthesis and upregulation of low density lipoprotein (LDL) receptors, consequently lowering plasma LDL concentrations. Statins treatment was associated with a statistically significant 12% reduction in all-cause mortality. Statin therapy reduce the 5-year incidence of major coronary events safely, HMG CoA reductase inhibition can also reduce inflammation[1–2].

As the world population continues to grow and aging, the global burden of cancer continues to increase particularly in developing countries. BC is the most frequently diagnosed cancer and the leading cause of cancer death among the female population, accounting for 23% of the total cancer cases and 14% of the cancer deaths[3].

Early studies in animal models raised concerns that statins may have carcinogenic properties. The results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except for patients with a high short-term risk of coronary heart disease[4]. Contrary to early concerns over the carcinogenicity of statins, a growing body of evidence suggests statins may in fact have a chemopreventive potential against cancer. Some studies have reported that statin use is inversely related to BC while others have reported null or positive associations. Many of the epidemiology studies on statin use and BC risk lacked information on potential confounders such as diet, level of physical activity, and BC screening behavior. There are many meta-analyses published on this issue recently, but the data are unsatisfactory for recommending statins for primary BC prevention. Furthermore, its secondary prevention is not well studied[5]. Recently, Undela et al conducted a detailed meta-analysis including 24 observational studies published regarding this subject. Their findings did not support the hypothesis that statins have a protective effect against BC[6]. Thus, the present meta-analysis of available data was conducted to comprehensively evaluate the association between fluvastatin and BC risk.

METHODS

Search strategy

Pubmed database were searched up to January 1, 2015 to identify potentially relevant publications, the reference lists of these relevant publications and review articles were screened. If necessary, correspondent authors were contacted to obtain the original experimental data. All potentially relevant articles (include the titles, abstracts, and/or full texts) were reviewed by two investigators(ZJ and LDM) independently to determine whether they were in accordance with the inclusion and exclusion criteria, and the divergence resolved through discussion or by another investigator(ZW). Search

terms were used as follows: ("hydroxymethylglutaryl-coa reductase inhibitors" OR "statins" OR "fluvastatin") AND ("neoplasms" OR "tumor"). The following information were extracted from all the selected articles: first author's name, year of publication, country of the population studied, study period, RR estimates and 95% CIs.

Inclusion and exclusion criteria, and quality assessment

Inclusion and exclusion criteria were as follows: inclusion criteria were 1.observational studies (cohort or case-control) 2. evaluated exposure/outcome to fluvastatin and risk of BC. 3. original article offered RR/OR/HR. 4. published in English. Exclusion criteria were 1. reviews, letters to the editor without original data, editorials and case reports. 2. not humans. 3. duplicated data (Figure 1). All cohort and case-control studies were assessed based on Newcastle-Ottawa Scale (NOS) for quality assessment. In this scale, observational studies were scored across three categories: population selection (four questions); comparability of study groups(two questions); ascertainment of the exposure/outcome of interest (three questions), high-quality study defined as score ≥ 7 [7].

Statistical analysis

Since outcomes of BC were relatively rare, Odds Ratio (OR) and Hazard Ratio (HR) were considered similarly as RR, the RR of statins therapy group versus non-statins therapy group were calculated for pooled RR, all statistical analysis were conducted using STATA version12.0 (Stata Corporation, College Station, TX, USA). Dichotomous data results were summarized using RR and 95% CIs as the effect size. Heterogeneity among studies was assessed by the Cochrane Chi-square Q test and I^2 test, $P < 0.1$ and $I^2 > 50\%$ was considered to be statistically significant, a fixed effect model (Mantel-Haenszel) was used to pool the data when no significant heterogeneity was found. Otherwise, the random effect model (DerSimonian-Laird) was used. The significance of the pooled RR was determined by the Z-test, and $P < 0.05$ was considered statistically significant. This meta-analysis was performed and reported in accordance with the PRISMA guidelines for systematic reviews and meta-analyses[12].

RESULTS

Meta-analysis result

Four studies (Table 1) contributed to the meta-analysis, process of screening flow diagram as in Figure 1, and quality assessment as in Table 2, findings from the studies were listed in Table 3. All case-control studies reported OR and the cohort study reported RR/HR. The overall RR of BC risk for fluvastatin use was 0.74, 95 % CI = 0.58, 0.95. Fluvastatin seems negatively correlated with BC risk. No significant heterogeneity ($P_{heterogeneity}$=0.289, I^2 = 20.1%) was observed (Figure 2).

Sensitivity analysis and publication bias

To evaluate the stability of the combined results, sensitivity analysis was conducted (Figure 3). Significant variation in combined RR was observed by excluding Pocobelli 2008[9]. As only 4 studies were included in the present meta-analysis, funnel plot and begg's test were not conducted.

DISCUSSION

Statins use has increased dramatically in the past decade. Association between use of statins and cancer risk was controversial in all the previous meta-analysis studies[13–17]. The present meta-analysis supports the hypothesis that fluvastatin use is negatively correlated with BC risk, and no significant heterogeneity was observed.

Contrary to early concerns over the carcinogenicity of statins, new experimental evidence suggests statins' chemopreventive potential against cancer. Statins inhibited the HMG CoA reductase, then interfered with the rate-limiting step of the mevalonate pathway, which led to reduced levels of mevalonate and its downstream products. Many of these products participated in critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell

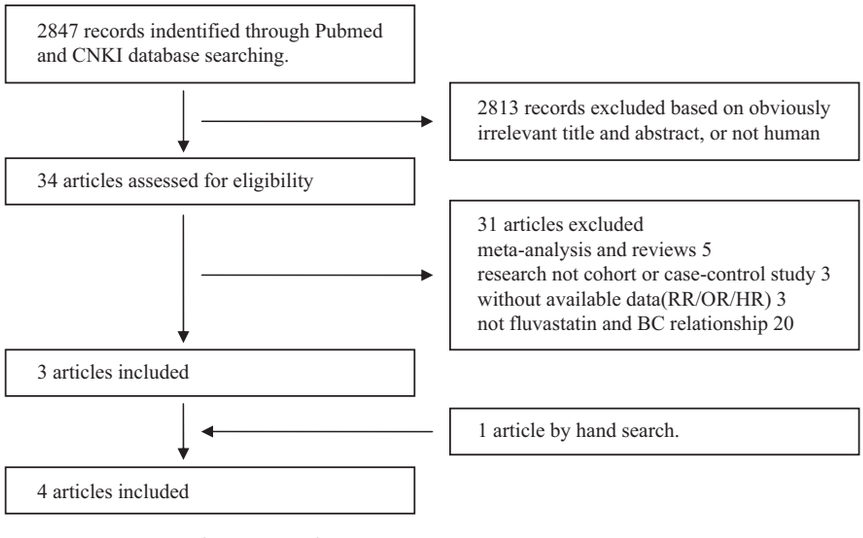

Figure 1. Flow diagram showing the process of screening references.

Table 1. Characteristics of studies included in the meta-analysis

Study (year)	populations	Design	Study period	age, y
Hippisley 2010[8]	UK	CC	2004–2011	>50
Boudreau 2004[9]	US	CC	1997–1999	65–79
Pocobelli 2008[10]	US	CC	2005–2008	>50
Cauley 2006[11]	US	CO	1993–2004	50–79

CC, case-control studies; CO, cohort studies; RR, relative risk; CI, confidence interval. UK, United Kindom. US, United States.

Table 2. Quality assessment of included studies by Newcastle–Ottawa scale

Study	Selection	Comparability	Outcome/ exposure	Total score
Hippisley 2010[8]	★★★	★★	★★★	8
Boudreau 2004[9]	★★★	★	★★★	7
Pocobelli 2008[10]	★★★★	★★	★★	8
Cauley 2006[11]	★★	★★	★★	6

cycle progression. Perturbations of these processes in neoplastic cells by the statins may result in restraint tumor initiation, growth, and metastasis[18].

Nowadays, alterations of lipid metabolism have become increasingly recognized as a hallmark of cancer cells. Accumulated in vitro and in vivo clinical evidence points out that statins in a variety of human malignancies, in regulating tumor cell growth and anti-tumor immune response[19–24]. For example, statins block HMG-CoA reductase, control hypercholesterolemia and target the mevalonate pathway (MVA), and induced apoptosis in multiple myeloma and acute myeloid leukemia cell lines[25]. Lipophilic statins, such as lovastatin may present a promising therapeutic option for treatment of aggressive human paragangliomas by inducing apoptosis and inhibiting tumor spread via decreased phosphorylation of mitogen-activated kinase (MAPK) pathway[26]. Also, Lovastatin inhibited the growth of gastric cancer cells[27]. Simvastatin inhibited the viability of castration-resistant C4-2 cells. Significant decrease in cell viability and growth curve was observed in castration-resistant prostate cancer cells[28]. Thus, statins showed anticancer effects in various cell lines, including breast carcer cell lines[29–31].

Differences in hydrophilicity may have clinical significance with respect to cancer risk[5]. Experimental study have confirmed that fluvastatin is associated with cancer risk. Fluvastatin could inhibit in vitro growth of Renal cancer cells in a time and dose dependent manner, fluvastatin may effectively inhibit in vitro tumor growth, invasion, angiogenesis, and metastasis of Renal cancer cells[32]; It inhibited proliferation of PC-3 prostate cancer cell line and the androgen-dependent prostate cancer cell line by inducing a G1 arrest[33]. Fluvastatin induces apoptosis by inhibiting geranylgeranyl pyrophosphate (GGPP) biosynthesis and consequently decreasing the level of phosphorylated extracellular signal-regulated kinase (ERK 1/2) in human tongue carcinoma cell line, and it may be used as an anticancer agent for tongue carcinoma[34]. Fluvastatin inhibited proliferation of hepatocellular carcinoma (HCC) cell lines (HepG2, SMMC-7721 and MHCC-97H) by inducing apoptosis and G2/M phase arrest in a dose-dependent manner, and cell invasion assay results revealed that fluvastatin significantly decreased the invasion potency of HCC cells[35]. Fluvastatin decreased ERK1/2 expression, (caused a) reduction in the vascular endothelial growth factor (VEGF) concentrations, and inhibited C6 rat malignant glioma cells proliferation[36]. When rats (FLF1) were pretreated with fluvastatin, it had a dose-dependent inhibitory effect on primary and metastatic hepatocellular tumors. Its inhibitory effect on growth and pyruvate kinase (PK) activity in metastases were higher than in primary tumors[37].

Experimental studies also have confirmed that fluvastatin is negatively correlated with BC risk .Fluvastatin treatment enhanced the caspase-3–like activity and DNA fragmentation in breast cancer cell line MCF-7 cells, and significantly inhibited the proliferation, inducible nitric oxide synthase (iNOS)-mediated nitric oxide (NO) is responsible in part for the proapoptotic, tumoricidal, and antiproliferative effects of statins in MCF-7 cells[38]; Fluvastatin showed measurable biologic changes by reducing tumor proliferation (Ki-67) and increasing apoptotic activity (cleaved caspase-3) in high-grade breast cancer[39]. The antineoplastic effects of fluvastatin in the chemoprevention of N-methyl-N-nitrosourea-induced mammary carcinogenesis in female rats were evaluated. It found fluvastatin at higher concentrations suppressed tumor frequency and tumor incidence[40]. When 4T1/luc mouse, a breast cancer model treated with fluvastatin, a significant reduction in progression of established metastases and increased survival of mice were observed. Fluvastatin is a

Table 3. Findings from studies included in the meta-analysis

Study (year)	RR	CI	adjustment
Hippisley 2010[8]	0.74	0.45–1.21	NA
Boudreau 2004[9]	1.1	0.6–2.1	age at reference date (5-year categories), reference year, county of residence, and use ofantihypertensive medication (yes, no).
Pocobelli 2008[10]	0.5	0.3–0.8	reference age, state of residence, reference year, first degree family history of breast cancer, menopausal status/age at menopause, parity/age at first birth, body mass index, time of postmenopausal hormone use, education, and screening mammography history
Cauley 2006[11]	0.8	0.53–1.19	body mass index, race, smoking, family history of breast cancer, education, hysterectomy, mammogram in the last 2 years, age at menarche, parity/age at first birth, alcohol use, percentage of calories from fat, physical activity, and nonsteroidal anti-inflammatory drug use

CC, case-control studies; CO, cohort studies; RR, relative risk; CI, confidence interval. NA, not available

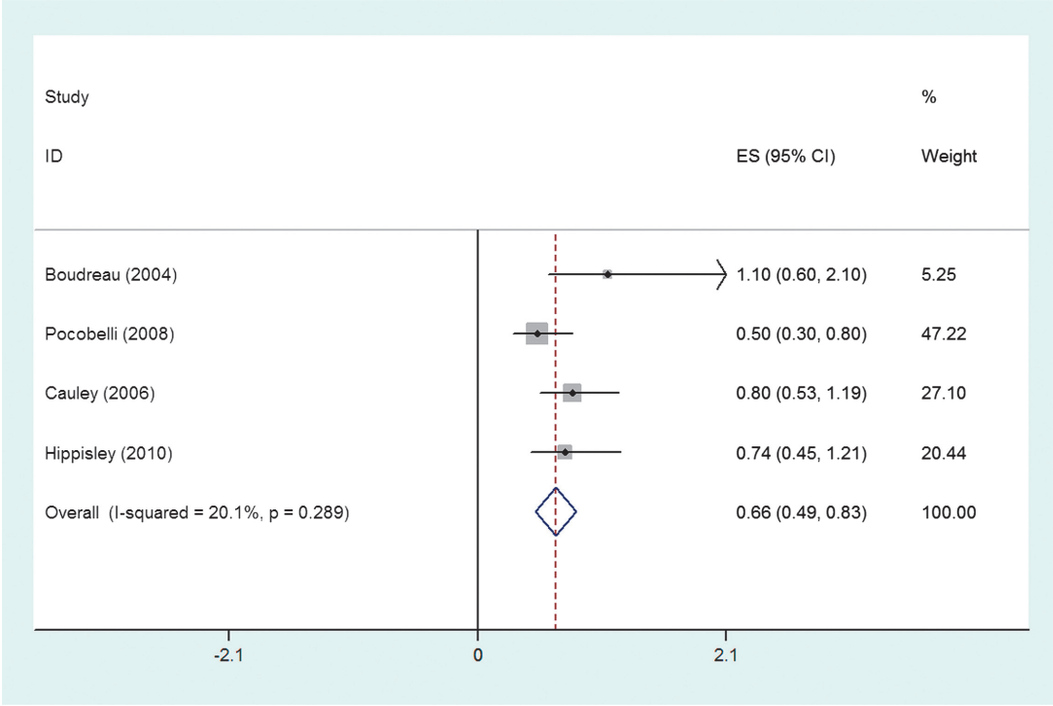

Figure 2. Fluvastatin and the risk of BC. Forest plot showed the association of fluvastatin and the risk of BC with fixed-effects model.

potential clinical drug for the treatment of established metastasis[41].

Present analysis result indicates that fluvastatin may decrease BC risk. Further high quality studies are needed to confirm this Finding.

In the present meta-analysis, there are following limitations to be concerned. First, neither unpublished studies nor original data were obtained. Second, literature search was restricted to the CNKI and Pubmed database. Finally, significant variation in combined RR was observed when the study by Pocobelli was excluded, more research is needed to enhance the stability of the analysis.

CONCLUSION

Findings from this meta-analysis indicate that fluvastatin use may reduce the risk of BC. Further high quality research is needed to confirm this finding and address the underlying biological mechanisms for this association.

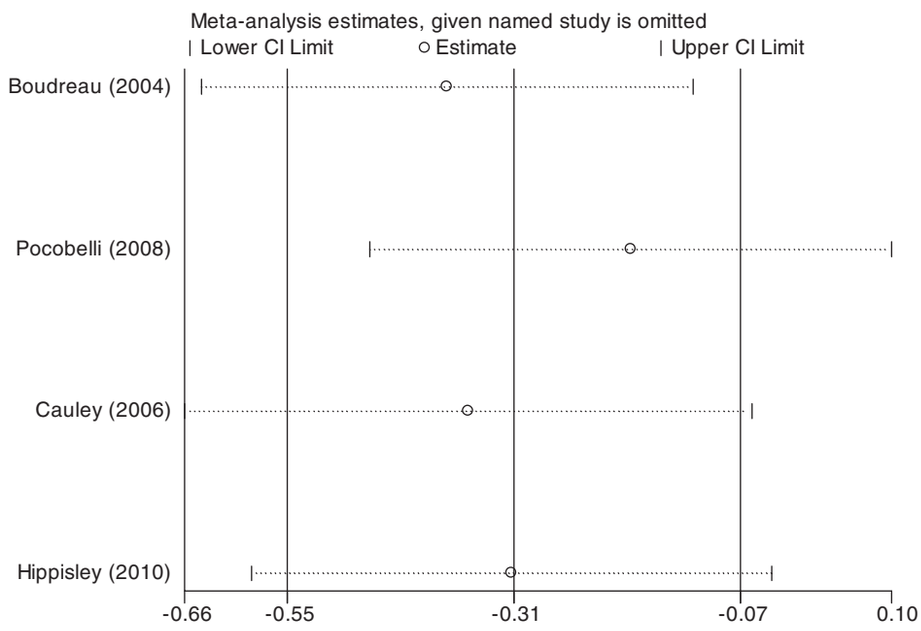

Figure 3. Sensitivity analysis for the association between fluvastatin and breast cancer.

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